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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  FEB 27   New STN AnaVist pricing effective March 1, 2006
 NEWS  4  MAY 10   CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS  5  MAY 11   KOREAPAT updates resume
 NEWS  6  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS  7  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS  8  MAY 30   The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02   The first reclassification of IPC codes now complete in
                   INPADOC
 NEWS 10  JUN 26   TULSA/TULSA2 reloaded and enhanced with new search and
                   and display fields
 NEWS 11  JUN 28   Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 12  JUl 11   CHEMSAFE reloaded and enhanced
 NEWS 13  JUl 14   FSTA enhanced with Japanese patents
 NEWS 14  JUl 19   Coverage of Research Disclosure reinstated in DWPI
 NEWS 15  AUG 09   INSPEC enhanced with 1898-1968 archive
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 NEWS 17  AUG 30   CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS 18  SEP 11   CA/CAplus enhanced with more pre-1907 records
 NEWS 19  SEP 21   CA/CAplus fields enhanced with simultaneous left and right
                   truncation
 NEWS 20  SEP 25   CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS 21  SEP 25   CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS 22  SEP 25   CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 23  SEP 28   CEABA-VTB classification code fields reloaded with new
                   classification scheme

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006..

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FILE 'HOME' ENTERED AT 02:53:18 ON 02 OCT 2006

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.63       0.63

FILE 'USPATFULL' ENTERED AT 02:55:22 ON 02 OCT 2006
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2006 (20060928/PD)
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REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

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=> e delmedico mary kay/in
E1            3     DELME ROGER ROBERT/IN
E2            2     DELMEDICO MARY K/IN
E3            1 --> DELMEDICO MARY KAY/IN
E4            1     DELMEDICO SUSAN G/IN
E5            2     DELMEE PETRUS H M/IN
E6            2     DELMEGE ARTHUR H/IN
E7            2     DELMEGE DALE/IN
E8            2     DELMEGE JAMES W/IN
E9            1     DELMENDO JON G/IN
E10           1     DELMENICO ANDREAS/IN
E11           1     DELMENICO JACK/IN
E12           4     DELMENICO PETER/IN

=> s e3
L1            1 "DELMEDICO MARY KAY"/IN

=> d l1,cbib,clm

L1   ANSWER 1 OF 1  USPATFULL on STN
2004:100776 HIV-derived HR1 peptides modified to form stable trimers, and their
    use in therapy to inhibit transmission of human immunodeficiency virus.
    Delmedico, Mary Kay, Raleigh, NC, UNITED STATES
    Dwyer, John, Chapel Hill, NC, UNITED STATES
    US 2004076637 A1 20040422
    APPLICATION: US 2003-664021  A1  20030916 (10)
    PRIORITY: US 2002-414514P  20020927 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A synthetic peptide comprising an amino acid sequence derived from
       the HR1 region of HIV-1 gp41; wherein the HR1 region consists of native
       amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof;
       wherein the HR1 region from which the synthetic peptide is derived
       comprises a hydrophobic domain of amino acids corresponding to amino
       acid residues in positions 28 to 36 of SEQ ID NO:1 or polymorphisms
       thereof; wherein the amino acid residues comprising the hydrophobic
       domain correspond to heptad repeat positions "efgabcdef"; and wherein
       the amino acid sequence of the synthetic peptide further comprises one
       or more amino acid substitutions in the heptad repeat positions
       "efgabcdef" comprising the hydrophobic domain, as compared to the native
       amino acid sequence of the HR1 region, which enables synthetic peptide
       to self-assemble in solution into trimers.

       2. The synthetic peptide according to claim 1, wherein the one or more
       amino acid substitutions in the hydrophobic domain comprise either a
       substitution in the "c" position, or a substitution in both the "g"
       position and the "c" position, of the heptad repeat positions
       "efgabcdef".
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3. The synthetic peptide according to claim 2, wherein the synthetic peptide comprises an amino acid substitution additional to a substitution in either the "c" position or both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

4. The synthetic peptide according to claim 1, wherein the one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" are in a position of the heptad repeat positions selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

5. The synthetic peptide according to claim 4, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

6. The synthetic peptide according to claim 1, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

7. The synthetic peptide according to claim 2, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

8. The synthetic peptide according to claim 3, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

9. The synthetic peptide according to claim 4, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

10. The synthetic peptide according to claim 5, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide,

and a combination thereof.

11. A trimer formed from synthetic peptide according to claim 1.

12. The trimer according to claim 11, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

13. A trimer formed from synthetic peptide according to claim 2.

14. The trimer according to claim 13, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

15. A trimer formed from synthetic peptide according to claim 3.

16. The trimer according to claim 15, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

17. A trimer formed from synthetic peptide according to claim 4.

18. The trimer according to claim 17, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

19. A trimer formed from synthetic peptide according to claim 5.

20. The trimer according to claim 19, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

21. A synthetic peptide comprising an amino acid sequence derived from the HR1 region of HIV-1 gp41; wherein the amino acid sequence comprises a heptad repeat containing a plurality of heptads, and a hydrophobic domain comprising heptad repeat positions "efgabcdef" corresponding to amino acids 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the synthetic peptide comprises an amino acid substitution in either the "c" position of the hydrophobic domain, or in both the "g" position and the "c" position of the hydrophobic domain, as compared to native sequence of the HR1 region; wherein the amino acid substitution enables the synthetic peptide to self-associate in solution into trimers.

22. The synthetic peptide according to claim 21, wherein the synthetic peptide comprises an amino acid substitution, as compared to native sequence of the HR1 region, additional to a substitution in a "c" position or in both the "g" position and "c" position; wherein the additional amino acid substitution is in one or more heptads of the synthetic peptide; and wherein the additional amino acid substitution is in one or more amino acid positions selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

23. The synthetic peptide according to claim 21, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

24. The synthetic peptide according to claim 22, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

25. A trimer formed from synthetic peptide according to claim 21.

26. The trimer according to claim 25, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

27. A trimer formed from synthetic peptide according to claim 22.

28. The trimer according to claim 27, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

29. A synthetic peptide comprising an amino acid sequence derived from the HR1 region of HIV-1 gp41; wherein the amino acid sequence comprises a heptad repeat containing a plurality of heptads, and a hydrophobic domain comprising heptad repeat positions "efgabcdef" corresponding to amino acids 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the synthetic peptide comprises an amino acid substitution in one or more of an "e" position at the C-terminus of the hydrophobic domain, an "f" position at the C-terminus of the hydrophobic domain, or a combination thereof, as compared to native sequence of the HR1 region; and wherein the amino acid substitution enables the synthetic peptide to self-associate in solution into trimers.

30. The synthetic peptide according to claim 29, wherein the synthetic peptide comprises an amino acid substitution, as compared to native sequence of the HR1 region, additional to the substitution in one or

more of an "e" position and "f" position; wherein the additional amino acid substitution is in one or more heptads of the synthetic peptide; and wherein the additional amino acid substitution is in one or more amino acid positions selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

31. The synthetic peptide according to claim 29, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

32. The synthetic peptide according to claim 30, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

33. A trimer formed from synthetic peptide according to claim 29.

34. The trimer according to claim 33, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

35. A trimer formed from synthetic peptide according to claim 30.

36. The trimer according to claim 35, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

37. A synthetic peptide comprising an amino acid sequence selected from the group of amino acid sequences consisting of: SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:81, and SEQ ID NO:82.

38. The synthetic peptide according to claim 37, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

39. A trimer formed from synthetic peptide according to claim 37.

40. The trimer according to claim 39, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less

than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

41. A trimer formed from self-association of synthetic peptide in solution, wherein the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; wherein the HR1 region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; wherein the HR1 region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids corresponding to amino acid residues 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and wherein the amino acid sequence of the synthetic peptide further comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to native amino acid sequence of the HR1 region, which enables synthetic peptide to self-associate in solution into trimers.

42. The trimer according to claim 39, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

43. A trimer formed from self-association of synthetic peptide in solution, wherein the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; wherein the amino acid sequence comprises a heptad repeat containing a plurality of heptads, and a hydrophobic domain comprising heptad repeat positions "efgabcdef" corresponding to amino acids 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the synthetic peptide comprises an amino acid substitution in either the "c" position of the hydrophobic domain, or in both the "g" position and the "c" position of the hydrophobic domain, as compared to native sequence of the HR1 region; and wherein the amino acid substitution enables the synthetic peptide to self-associate in solution into trimers.

44. The trimer according to claim 43, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

45. A trimer formed from self-association of synthetic peptide in solution, wherein the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; wherein the amino acid sequence comprises a heptad repeat containing a plurality of heptads, and a hydrophobic domain comprising heptad repeat positions "efgabcdef" corresponding to amino acids 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the synthetic peptide comprises an amino acid substitution in either the "c" position of the hydrophobic domain or in both the "g" position and the "c" position of the hydrophobic domain, as compared to native sequence of the HR1 region; wherein the synthetic peptide also comprises an amino acid substitution, additional to the substitution in the "c" position or in both the "g" position and "c" position, in one or more heptads of the synthetic peptide; wherein the additional amino acid substitution is in one or more amino acid

positions selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof; and wherein the amino acid substitutions enable the synthetic peptide to self-associate in solution into trimers.

46. The trimer according to claim 45, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

47. A trimer formed from self-association of synthetic peptide in solution, wherein the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; wherein the amino acid sequence comprises a heptad repeat containing a plurality of heptads, and a hydrophobic domain comprising heptad repeat positions "efgabcdef" corresponding to amino acids 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the synthetic peptide comprises an amino acid substitution in one or more of an "e" position at the C-terminus of the hydrophobic domain, an "f" position at the C-terminus of the hydrophobic domain, or a combination thereof, as compared to native sequence of the HR1 region; and wherein the amino acid substitution enables the synthetic peptide to self-associate in solution into trimers.

48. The trimer according to claim 47, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

49. A trimer formed from self-association of synthetic peptide in solution, wherein the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; wherein the amino acid sequence comprises a heptad repeat containing a plurality of heptads, and a hydrophobic domain comprising heptad repeat positions "efgabcdef" corresponding to amino acids 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the synthetic peptide comprises an amino acid substitution in one or more of an "e" position at the C-terminus of the hydrophobic domain, an "f" position at the C-terminus of the hydrophobic domain, or a combination thereof, as compared to the native sequence of the HR1 region; wherein the synthetic peptide also comprises an amino acid substitution, additional to the substitution in either or both of the "e" position and the "f" position, in one or more heptads of the synthetic peptide; wherein the additional amino acid substitution is in one or more amino acid positions selected from the group consisting of an "a" position, a "d" position, a "b" position", and a combination thereof; and wherein the amino acid substitutions enable the synthetic peptide to self-associate in solution into trimers.

50. The trimer according to claim 49, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

51. A trimer formed from self association of synthetic peptide in

solution, wherein the synthetic peptide comprises an amino acid sequence selected from the group of amino acid sequences consisting of: SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:81, and SEQ ID NO:82.

52. The trimer according to claim 49, further comprising a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimer, and a combination thereof.

53. A method for inhibition of transmission of HIV-1 to a cell comprising contacting the virus, in the presence of a target cell, with synthetic peptide in a concentration effective to inhibit infection of the cell by HIV-1, thereby inhibiting transmission of HIV-1 to the cell, wherein: the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; the HR1 region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; the HR1 region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids comprising the sequence corresponding to amino acid residues 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the HR1 region, which enables synthetic peptide to self-assemble in solution into trimers.

54. The method according to claim 53, wherein the one or more amino acid substitutions in the hydrophobic domain comprise a substitution in either the "c" position or in both the "g" position and the "c" position of the heptad repeat positions "efgabcdef".

55. The method according to claim 54, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in either the "c" position or in both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

56. The method according to claim 53, wherein the one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" are selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

57. The method according to claim 56, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

58. The method according to claim 53, wherein synthetic peptide further comprises a component selected from the group consisting of one or more

reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

59. The method according to claim 53, wherein synthetic peptide is in an oligomeric form comprising trimers.

60. The method according to claim 59, wherein the trimers further comprise a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimers, and a combination thereof.

61. The method of claim 53, wherein the synthetic peptide is parenterally administered to an individual.

62. A method for inhibition of transmission of HIV-1 to a target cell comprising adding synthetic peptide to the virus and a target cell in an amount effective to inhibit infection of the cell by HIV-1, wherein: the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; the HR1 region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; the HR1 region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids comprising the sequence corresponding to amino acid residues 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the HR1 region, which enables synthetic peptide to self-assemble in solution into trimers.

63. The method according to claim 62, wherein the one or more amino acid substitutions in the hydrophobic domain comprise a substitution in either the "c" position, or in both the "g" position and the "c" position, of the heptad repeat positions "efgabcdef".

64. The method according to claim 63, wherein the synthetic peptide comprises an amino acid substitution additional to a substitution in either the "c" position or both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

65. The method according to claim 62, wherein the one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" are selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

66. The method according to claim 65, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group

consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

67. The method according to claim 62, wherein synthetic peptide further comprises a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

68. The method according to claim 62, wherein synthetic peptide is in an oligomeric form comprising trimers.

69. The method according to claim 68, wherein the trimers further comprise a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimers, and a combination thereof.

70. The method of claim 62, wherein synthetic peptide is parenterally administered to an individual.

71. A method for inhibiting HIV fusion with a target cell comprising contacting the virus, in the presence of a target cell, with synthetic peptide in a concentration effective to inhibit membrane fusion between the virus and the cell, wherein: the synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; the HR1 region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; the HR1 region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids comprising the sequence corresponding to amino acid residues 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the HR1 region, which enables synthetic peptide to self-assemble in solution into trimers.

72. The method according to claim 71, wherein the one or more amino acid substitutions in the hydrophobic domain comprise a substitution in either the "c" position or in both the "g" position and the "c" position of the heptad repeat positions "efgabcdef".

73. The method according to claim 72, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in the "c" position or in both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

74. The method according to claim 71, wherein the one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" are selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

75. The method according to claim 74, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

76. The method according to claim 71, wherein synthetic peptide further comprises a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

77. The method according to claim 71, wherein synthetic peptide is in an oligomeric form comprising trimers.

78. The method according to claim 77, wherein the trimers further comprise a component selected from the group consisting of one or more reactive functionalities, a pharmaceutically acceptable carrier, a macromolecular carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of synthetic peptide forming the trimers, and a combination thereof.

79. The method of claim 71, wherein synthetic peptide is parenterally administered to an individual.

```
=> e dwyer john/in
E1            3     DWYER JEFF/IN
E2            6     DWYER JENNIFER SUE/IN
E3            6 --> DWYER JOHN/IN
E4            1     DWYER JOHN A/IN
E5            1     DWYER JOHN E/IN
E6            1     DWYER JOHN EDWARD JR/IN
E7           18     DWYER JOHN J/IN
E8            1     DWYER JOHN JAMES/IN
E9            1     DWYER JOHN MICHAEL/IN
E10           1     DWYER JOHN R/IN
E11           1     DWYER JOHN ROBERT/IN
E12           1     DWYER JOSEPH G/IN

=> s e3-e11
              6 "DWYER JOHN"/IN
              1 "DWYER JOHN A"/IN
              1 "DWYER JOHN E"/IN
              1 "DWYER JOHN EDWARD JR"/IN
             18 "DWYER JOHN J"/IN
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              1 "DWYER JOHN MICHAEL"/IN
              1 "DWYER JOHN R"/IN
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L2           31 ("DWYER JOHN"/IN OR "DWYER JOHN A"/IN OR "DWYER JOHN E"/IN OR
                 "DWYER JOHN EDWARD JR"/IN OR "DWYER JOHN J"/IN OR "DWYER JOHN
                JAMES"/IN OR "DWYER JOHN MICHAEL"/IN OR "DWYER JOHN R"/IN OR
                "DWYER JOHN ROBERT"/IN)
```

```
=> s l2 and (HR1 or HR2)
           521 HR1
           432 HR2
L3  .        2 L2 AND (HR1 OR HR2)

=> s l3 not l1
L4           1 L3 NOT L1

=> d l4,cbib,clm

L4   ANSWER 1 OF 1  USPATFULL on STN
2004:120446 Method for production of antivirals by use of HIV-derived HR1
    peptides, and trimers formed therefrom.
    Dwyer, John, Chapel Hill, NC, UNITED STATES
    Delmedico, Mary K., Raleigh, NC, UNITED STATES
    US 2004091855 A1 20040513
    APPLICATION: US 2003-671316  A1  20030924 (10)
    PRIORITY: US 2002-414515P  20020927 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A method for identifying a compound that inhibits transmission of HIV
       to a target cell, the method comprising contacting synthetic peptide
       comprising trimers in the presence of a compound and with HR2 peptide
       under conditions and for a time sufficient to allow formation of a
       complex between the synthetic peptide comprising trimers and HR2
       peptide in vitro; and detecting the amount of complex formed; wherein
       inhibition or reduction of complex formation in the presence of the
       compound, as compared to complex formation in the absence of the
       compound, is indicative of ability of the compound to inhibit
       transmission of HIV to a target cell; and  wherein synthetic peptide
       comprises an amino acid sequence derived from the HR1 region of HIV-1
       gp41; wherein the HR1 region consists of native amino acid sequence
       shown as SEQ ID NO:1 or polymorphisms thereof; wherein the HR1 region
       from which the synthetic peptide is derived comprises a hydrophobic
       domain of amino acids corresponding to amino acid residues in positions
       28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the amino acid
       residues comprising the hydrophobic domain correspond to heptad repeat
       positions "efgabcdef"; and wherein the amino acid sequence of the
       synthetic peptide further comprises one or more amino acid substitutions
       in the heptad repeat positions "efgabcdef" comprising the hydrophobic
       domain, as compared to the native amino acid sequence of the HR1
       region, which enables synthetic peptide to self-assemble in solution
       into trimers.

       2. The method according to claim 1, wherein the amino acid sequence of
       the synthetic peptide comprises one or more amino acid substitutions in
       the hydrophobic domain comprising either a substitution in the "c"
       position, or a substitution in both the "g" position and the "c"
       position, of the heptad repeat positions "efgabcdef".

       3. The method according to claim 2, wherein the synthetic peptide
       comprises an amino acid substitution additional to a substitution in
       either the "c" position or both the "g" position and "c" position,
       wherein the additional amino acid substitution is in one or more amino
       acid positions of one or more heptads of the synthetic peptide, and
       wherein the one or more amino acid positions is selected from the group
       consisting of an "a" position, a "d" position, a "b" position, and a
       combination thereof.

       4. The method according to claim 1, wherein the amino acid sequence of
       the synthetic peptide comprises one or more amino acid substitutions in
```

the hydrophobic domain comprising the heptad repeat positions "efgabcdef" that are in a position of the heptad repeat positions selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

5. The method according to claim 4, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

6. The method according to claim 1, wherein the synthetic peptide further comprises a component selected from the group consisting of one or more reactive functionalities, a macromolecular carrier, a pharmaceutically acceptable carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

7. The method according to claim 1, wherein the synthetic peptide is predominately in trimeric form.

8. The method according to claim 1, wherein the synthetic peptide is in a monomer-trimer equilibrium.

9. A method for producing a drug that inhibits transmission of HIV to a target cell, the method comprising contacting synthetic peptide comprising trimers in the presence of a compound and with **HR2** peptide under conditions and for a time sufficient to allow formation of a complex between the synthetic peptide comprising trimers and **HR2** peptide in vitro; and detecting the amount of complex formed; wherein inhibition or reduction of complex formation in the presence of the compound is indicative of ability of the compound to inhibit transmission of HIV to a target cell; and wherein the drug comprises the compound contacted with a pharmaceutically acceptable carrier in producing the drug; and wherein synthetic peptide comprises an amino acid sequence derived from the **HR1** region of HIV-1 gp41; wherein the **HR1** region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; wherein the **HR1** region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids corresponding to amino acid residues in positions 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and wherein the amino acid sequence of the synthetic peptide further comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the **HR1** region, which enables synthetic peptide to self-assemble in solution into trimers.

10. The method according to claim 9, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising either a substitution in the "c" position, or a substitution in both the "g" position and the "c" position, of the heptad repeat positions "efgabcdef".

11. The method according to claim 10, wherein the synthetic peptide comprises an amino acid substitution additional to a substitution in either the "c" position or both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino

acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

12. The method according to claim 9, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" that are in a position of the heptad repeat positions selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

13. The method according to claim 12, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

14. The method according to claim 9, wherein the synthetic peptide further comprising a component selected from the group consisting of one or more reactive functionalities, a macromolecular carrier, a pharmaceutically acceptable carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

15. The method according to claim 9, wherein the synthetic peptide is predominately in trimeric form.

16. The method according to claim 9, wherein the synthetic peptide is in a monomer-trimer equilibrium.

17. In a method for identifying or producing a molecule that can inhibit the binding between **HR1** and **HR2** regions of HIV gp41, the improvement which comprises: use of a trimer as a binding partner with **HR2** peptide in detecting in vitro the ability of the molecule to bind to an HR (heptad repeat) region of HIV gp41; wherein the trimer is comprised of synthetic peptide comprising an amino acid sequence derived from the **HR1** region of HIV-1 gp41; wherein the **HR1** region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; wherein the **HR1** region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids corresponding to amino acid residues in positions 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and wherein the amino acid sequence of the synthetic peptide further comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the **HR1** region, which enables synthetic peptide to self-assemble in solution into trimers.

18. The method according to claim 17, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising either a substitution in the "c" position, or a substitution in both the "g" position and the "c" position, of the heptad repeat positions "efgabcdef".

19. The method according to claim 18, wherein the synthetic peptide comprises an amino acid substitution additional to a substitution in

either the "c" position or both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

20. The method according to claim 17, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" that are in a position of the heptad repeat positions selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

21. The method according to claim 20, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

22. The method according to claim 17, wherein the synthetic peptide further comprising a component selected from the group consisting of one or more reactive functionalities, a macromolecular carrier, a pharmaceutically acceptable carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

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=> file wpids
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     8.29       8.92

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E1            1     DELME V/IN
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E4            1     DELMEDICO N/IN
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E10           1     DELMEGE A H/IN
E11           2     DELMEGE D/IN
E12           1     DELMEGE J/IN

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L5            4 "DELMEDICO M K"/IN

=> d l5,bib,ab,1-4

L5   ANSWER 1 OF 4  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   2005-522744 [53]   WPIDS
DNC  C2005-158663
TI   Novel synthetic peptides derived from heptad repeat 2 region of human
     immunodeficiency virus gp41, useful for treating and/or inhibiting
     transmission of human immunodeficiency virus to target cell.
DC   B04 D16
IN   DELMEDICO, M K; DWYER, J
PA   (TRIM-N) TRIMERIS INC
CYC  108
PI   WO 2005067960   A1 20050728 (200553)* EN   92
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT
            KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG
            ZM ZW
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            KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ
            OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
            US UZ VC VN YU ZA ZM ZW
ADT  WO 2005067960 A1 WO 2004-US42918 20041221
PRAI US 2004-534810P      20040107
AB   WO2005067960 A UPAB: 20050818
     NOVELTY - A synthetic peptide (I) comprising a 36 amino acid, 36 amino
     acid or 38 amino acid (SEQ ID No. 2, 3 or 4) sequence fully defined in the
     specification, where (I) is substituted with helix promoting amino acids,
     and charged amino acids to form ion pairs with oppositely charged amino
     acids in (I), to obtain (I) with improved biological activity, is new.
          DETAILED DESCRIPTION - A synthetic peptide (I) comprising an amino
     acid derived from a fully defined 36 amino acid, 36 amino acid or 38 amino
     acid (SEQ ID No. 2, 3 or 4) sequence given in the specification, where:
          (a) (I) additionally has several amino acid substitutions, as
     compared to the base sequence, the amino acid substitutions comprising one
     or more helix promoting amino acids, and several charged amino acids
     introduced to form ion pairs with oppositely charged amino acids in the
     amino acid sequence of (I);
          (b) (I) differs from the base sequence by addition of a several amino
     acids, in replacing amino acids in the base sequence, and the several
     amino acids have a helix promoting amino acid;
          (c) (I) differs from base sequence by several amino acid
     substitutions comprising one or more helix-promoting amino acids, and
     several charged amino acids, the charged amino acids form several ion
     pairs in (I);
          (d) (I) differs from the base sequence by the addition of several
     amino acids, in replacing the amino acids in the base sequence comprising
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one or more helix promoting amino acids, and several charged amino acids, spaced apart from oppositely charged amino acids in forming ion pairs, and where (I) demonstrates an improved biological activity, the improved biological activity comprising an increase in antiviral activity against an HIV strain that is resistant to a base sequence, and improved pharmacokinetic properties; or

(e) (I) has a 33-59 amino acid (SEQ ID No. 5-95) sequence fully defined in the specification.

An INDEPENDENT CLAIM is also included for a nucleotide sequence (II) encoding SEQ ID No. 5-95.

ACTIVITY - Anti-HIV.

No biological data given.

MECHANISM OF ACTION - Inhibits transmission of HIV to cells (claimed).

USE - (I) is useful as an active therapeutic substance in therapy of HIV infection, where (I) is useful as a part of a therapeutic regimen containing one or more additional antiviral agents for therapy of HIV infection. (I) is useful for manufacturing a medicament for a therapeutic application for treatment of HIV. (I) is useful for inhibiting a transmission of HIV to a cell, which involves contacting or adding the virus in the presence of cell with (I), to inhibit infection of the cell by HIV, where (I) is added as a component of a therapeutic regimen. (I) is useful for inhibiting HIV fusion, which involves contacting the virus in the presence of a cell with (I), to inhibit HIV fusion. (I) is useful for treating an HIV-infected individual, which involves administering (I) to the individual to enable an effect of achieving a therapeutic application chosen from reduction in the viral load of HIV, an increase in circulating CD4+ cell population and their combination, in the treated individual. (All claimed).

ADVANTAGE - (I) has an increased helicity or stability as compared to helicity or stability of the base sequence, and has improved biological activity (claimed).

DESCRIPTION OF DRAWING(S) - The figure is a schematic representation of HIV gp41 showing the heptad repeat 1 and 2 regions.

Dwg.1/2

L5 ANSWER 2 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2004-374930 [35] WPIDS

DNC C2004-140955

TI Identifying compound inhibiting HIV transmission to target cell, comprises contacting synthetic peptide in presence of compound with heptad repeat peptide to form complex and identifying compound based on inhibition of complex formation.

DC B04 D16

IN **DELMEDICO, M K**; DWYER, J

PA (DELM-I) DELMEDICO M K; (DWYE-I) DWYER J

CYC 1

PI US 2004091855 A1 20040513 (200435)* 35

ADT US 2004091855 A1 Provisional US 2002-414515P 20020927, US 2003-671316 20030924

PRAI US 2002-414515P 20020927; US 2003-671316 20030924

AB US2004091855 A UPAB: 20040603

NOVELTY - Identifying (M1) compound that inhibits transmission of HIV to target cell, comprising contacting synthetic peptide (I) in presence of compound and with heptad repeat (HR2) peptide for forming complex between (I) and HR2 peptide, and detecting amount of complex formed, where inhibition or reduction of complex formation in presence of compound, indicates inhibition of HIV to target cell, is new.

DETAILED DESCRIPTION - Identifying (M1) a compound that inhibits transmission of HIV to a target cell, comprises contacting a synthetic peptide (I) comprising trimers in the presence of a compound and with

heptad repeat (HR2) peptide under conditions and for a time sufficient to allow formation of a complex between (I) comprising trimers and HR2 peptide in vitro, and detecting the amount of complex formed, where inhibition or reduction of complex formation in the presence of the compound, as compared to complex formation in the absence of the compound, is indicative of ability of the compound to inhibit transmission of HIV to a target cell.

INDEPENDENT CLAIMS are also included for:

(1) producing (M2) a drug that inhibits transmission of HIV to a target cell, comprising carrying out the contacting and detecting steps of (M1), where inhibition or reduction of complex formation in the presence of compound is indicative of ability of the compound to inhibit transmission of HIV to a target cell, and the drug comprises the compound contacted with the carrier in producing the drug; and

(2) identifying or producing (M3) a molecule that inhibits the binding between HR1 and HR2 regions of HIV gp41, where the improvement involves use of a trimer as a binding partner with HR2 peptide in detecting in vitro the ability of the molecule to bind to an HR region of HIV gp41, where the trimer is comprised of (I).

ACTIVITY - Anti-HIV. No biological data given.

MECHANISM OF ACTION - Inhibitor of transmission of HIV to target cell (claimed); Inhibitor of interaction between HR1 and HR2 regions of HIV gp41; Vaccine.

In vitro analysis of molecules inhibiting binding interaction between HR1 and HR2 regions, was carried out as follows: About 20 micro l of solution containing desired concentration of molecule having ability to bind to trimers and either inhibit or disrupt HR1-HR2 binding interactions, were added. Reference standards, e.g. predetermined amounts of known inhibitor of HR1-HR2 binding interactions or no inhibitor, were added to other reaction wells not containing the molecule. To each reaction well 10 micro l of trimers formed from the synthetic peptide was added. After a sufficient time for the trimers to contact the molecule, 10 micro l of desired concentration of labeled HR2 peptide was added to the reaction wells. The result indicated inhibition of binding interaction between HR1 and HR2 regions by the molecule. The molecule was then subjected to in vitro infectivity assay against HIV-1. The IC50 of the molecule was found to be 0.002 micro g/ml.

USE - (M1) is useful for identifying a compound that inhibits transmission of HIV to a target cell (claimed). The synthetic peptide of (M1) is useful for producing antiviral agents having activity against HIV. The compound identified by (M1) is useful as an antiviral agent for HIV.

DESCRIPTION OF DRAWING(S) - The figure is a graph representing use of synthetic peptide and heptad repeat (HR2) peptide for producing molecule that inhibits binding between HR1 and HR2 sequences.

Dwg.5/5

L5 ANSWER 3 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2004-316084 [29] WPIDS

DNC C2004-119901

TI New synthetic peptide comprising an amino acid sequence derived from the HR1 region of HIV-1 gp41, useful for inhibiting transmission of HIV-1 to a cell.

DC B04 D16

IN **DELMEDICO, M K**; DWYER, J

PA (DELM-I) DELMEDICO M K; (DWYE-I) DWYER J; (TRIM-N) TRIMERIS INC

CYC 102

PI WO 2004029074 A2 20040408 (200429)* EN 94

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

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RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM
ZW
US 2004076637 A1 20040422 (200429)
AU 2003287011 A1 20040419 (200462)
AU 2003287011 A8 20051103 (200629)
ADT WO 2004029074 A2 WO 2003-US30286 20030926; US 2004076637 A1 Provisional US 2002-414514P 20020927, US 2003-664021 20030916; AU 2003287011 A1 AU 2003-287011 20030926; AU 2003287011 A8 AU 2003-287011 20030926
FDT AU 2003287011 A1 Based on WO 2004029074; AU 2003287011 A8 Based on WO 2004029074
PRAI US 2003-664021 20030916; US 2002-414514P 20020927
AB WO2004029074 A UPAB: 20040505
NOVELTY - A new synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41.

DETAILED DESCRIPTION - A new synthetic peptide comprises an amino acid sequence derived from the HR1 region of HIV-1 gp41; where the HR1 region consists of native 59-amino acid sequence or polymorphisms; where the HR1 region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids corresponding to amino acid residues in positions 28 to 36 of 59-amino acid sequence or its polymorphisms; where the amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions efgabcdef; and where the amino acid sequence of the synthetic peptide further comprises one or more amino acid substitutions in the heptad repeat positions efgabcdef comprising the hydrophobic domain, as compared to the native amino acid sequence of the HR1 region, which enables synthetic peptide to self-assemble in solution into trimers.

INDEPENDENT CLAIMS are also included for the following:
(1) a trimer formed from synthetic peptide;
(2) a method for inhibiting transmission of HIV-1 to a cell;
(3) a method for inhibiting transmission of HIV-1 to a target cell; and
(4) a method for inhibiting HIV fusion with a target cell.

ACTIVITY - Anti-HIV. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The synthetic peptide is useful for inhibiting transmission of HIV-1 to a cell (claimed).

Dwg.0/4

L5 ANSWER 4 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2001-514829 [56] WPIDS
DNC C2001-153937
TI Heptad repeat region peptide analogs useful for inhibiting virus/cells fusion, useful for treating HIV and Respiratory Syncytial Virus infection.
DC B04
IN ANTCZAK, J B; DELMEDICO, M K; ERICKSON, J B; LAMBERT, D M; SISTA, P
PA (TRIM-N) TRIMERIS INC
CYC 94
PI WO 2001064013 A2 20010907 (200156)* EN 584
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AU 2001036753 A 20010912 (200204)
US 6623741 B1 20030923 (200364)
ADT WO 2001064013 A2 WO 2001-US3988 20010207; AU 2001036753 A AU 2001-36753 20010207; US 6623741 B1 US 2000-515965 20000229
FDT AU 2001036753 A Based on WO 2001064013

PRAI US 2000-515965 20000229
AB WO 200164013 A UPAB: 20011001
NOVELTY - Isolated heptad repeat region analog peptides (designated DP178 and DP107) comprising amino acid sequence selected from (A1)-(A9) (given in the specification) , are new. DP178 and DP107 correspond to amino acids 638-673 and 558-595 of HIV-1LAI transmembrane protein gp41 (heptad repeat region HR2 and HR1), respectively.

DETAILED DESCRIPTION - An isolated peptide comprising an amino acid sequence selected from (A1)-(A9).

INDEPENDENT CLAIMS are also included for the following:

(1) a method (II) for inhibiting Respiratory Syncytial Virus (RSV) infection in a cell, comprising contacting the cell with a peptide comprising (A1)-(A9) (i.e. (I)) so that infection is inhibited;

(2) a method (III) for identifying a compound that inhibits formation or disrupts a DP107-like/DP178-like complex, comprising:

(a) contacting, in the presence and absence of a test compound:

(i) a peptide comprising a DP178-like amino acid sequence; and

(ii) a second peptide comprising (A1)-(A9) (i.e. (I)); and

(b) determining the binding affinity of the first peptide for the second peptide both in the presence and in the absence of the test compound (a lower binding affinity in the presence of the test compound indicates that the test compound inhibits formation of a DP107-like/DP178-like complex).

X-VLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSK-Z (A1)
X-VLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYI-Z (A2)
X-VLHLEGEVNKIKSALLSINKAVVSLSNGVSVLTSKVLDLKNYID-Z (A3)
X-VLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDK-Z (A4)
X-VLHLEGEVNKIKSALLSINKAVVSLSNGVSVLTSKVLDLKNYIDKQ-Z (A5)
X-SKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ-Z (A6)
X-AVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ-Z (A7)
X-AVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQL-Z (A8)
X-SGVAAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIIDKQL-Z (A9)

X = an amino group, an acetyl group, a 9-flurenylmethoxy-carbonyl group, a hydrophobic group or a macromolecular carrier group; and

Z = a carboxy group, an amido group, a hydrophobic group or a macromolecular carrier group.

ACTIVITY - Virucidal.

MECHANISM OF ACTION - The peptide analogs interfere with DP107-like/DP178-like complexes and therefore prevent the virus fusing with the host cell.

An antiviral assay was conducted by adding test peptides in 3% Eagle's Minimal Essential Medium (EMEM) and 100/well RSV-infected Hep-2 cells to wells containing uninfected Hep-2 cells. The well were then incubated at 37 deg. C for 48 hours. After incubation cells in control wells were checked for fusion centers. Media was removed from the wells, followed by addition, to each well, of 50 micro g 25% Crystal Violet stain in methanol. The cells were rinsed immediately and allowed to dry. The number of syncytia were then counted using a dissecting microscope. The IC50 values obtained indicated that the peptides tested, T1584, T1623, T1583 and T1581 were potent inhibitors of RSV with IC50 values of 0.23, 0.8, 1.09, 3.36 micro g/ml, respectively.

USE - The peptides may be used to inhibit Respiratory Syncytial Virus (RSV) infection in a cell (claimed). They may also be used to inhibit HIV infection.

Dwg.0/34

=> e dwyer john/in
E1 10 DWYER J W/IN
E2 1 DWYER JJ/IN
E3 0 --> DWYER JOHN/IN
E4 1 DWYER JOYCE R S/IN

```
E5            3     DWYER K/IN
E6           13     DWYER K A/IN
E7            1     DWYER K D/IN
E8            2     DWYER K F/IN
E9            2     DWYER K K/IN
E10           2     DWYER L/IN
E11           1     DWYER L A/IN
E12           1     DWYER L D/IN

=> e dwyer j/in
E1            2     DWYER HALLQUIST P/IN
E2            1     DWYER I N/IN
E3           13 --> DWYER J/IN
E4            1     DWYER J A/IN
E5            2     DWYER J C/IN
E6            5     DWYER J E/IN
E7            3     DWYER J F/IN
E8            1     DWYER J G/IN
E9           23     DWYER J J/IN
E10           2     DWYER J L/IN
E11           2     DWYER J M/IN
E12           7     DWYER J P/IN

=> s e3
L6           13 "DWYER J"/IN

=> s l6 and (HR1 or HR2)
           162 HR1
           151 HR2
L7           2 L6 AND (HR1 OR HR2)

=> d l7,bib,ab,1-2

L7   ANSWER 1 OF 2  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   2004-374930 [35]   WPIDS
DNC  C2004-140955
TI   Identifying compound inhibiting HIV transmission to target cell, comprises
     contacting synthetic peptide in presence of compound with heptad repeat
     peptide to form complex and identifying compound based on inhibition of
     complex formation.
DC   B04 D16
IN   DELMEDICO, M K; DWYER, J
PA   (DELM-I) DELMEDICO M K; (DWYE-I) DWYER J
CYC  1
PI   US 2004091855   A1 20040513 (200435)*      35
ADT  US 2004091855 A1 Provisional US 2002-414515P 20020927, US 2003-671316
     20030924
PRAI US 2002-414515P      20020927; US 2003-671316       20030924
AB   US2004091855 A UPAB: 20040603
     NOVELTY - Identifying (M1) compound that inhibits transmission of HIV to
     target cell, comprising contacting synthetic peptide (I) in presence of
     compound and with heptad repeat (HR2) peptide for forming complex
     between (I) and HR2 peptide, and detecting amount of complex formed,
     where inhibition or reduction of complex formation in presence of
     compound, indicates inhibition of HIV to target cell, is new.
          DETAILED DESCRIPTION - Identifying (M1) a compound that inhibits
     transmission of HIV to a target cell, comprises contacting a synthetic
     peptide (I) comprising trimers in the presence of a compound and with
     heptad repeat (HR2) peptide under conditions and for a time sufficient
     to allow formation of a complex between (I) comprising trimers and HR2
     peptide in vitro, and detecting the amount of complex formed, where
```

inhibition or reduction of complex formation in the presence of the compound, as compared to complex formation in the absence of the compound, is indicative of ability of the compound to inhibit transmission of HIV to a target cell.

INDEPENDENT CLAIMS are also included for:

(1) producing (M2) a drug that inhibits transmission of HIV to a target cell, comprising carrying out the contacting and detecting steps of (M1), where inhibition or reduction of complex formation in the presence of compound is indicative of ability of the compound to inhibit transmission of HIV to a target cell, and the drug comprises the compound contacted with the carrier in producing the drug; and

(2) identifying or producing (M3) a molecule that inhibits the binding between **HR1** and **HR2** regions of HIV gp41, where the improvement involves use of a trimer as a binding partner with **HR2** peptide in detecting in vitro the ability of the molecule to bind to an HR region of HIV gp41, where the trimer is comprised of (I).

ACTIVITY - Anti-HIV. No biological data given.

MECHANISM OF ACTION - Inhibitor of transmission of HIV to target cell (claimed); Inhibitor of interaction between **HR1** and **HR2** regions of HIV gp41; Vaccine.

In vitro analysis of molecules inhibiting binding interaction between **HR1** and **HR2** regions, was carried out as follows: About 20 micro l of solution containing desired concentration of molecule having ability to bind to trimers and either inhibit or disrupt **HR1-HR2** binding interactions, were added. Reference standards, e.g. predetermined amounts of known inhibitor of **HR1-HR2** binding interactions or no inhibitor, were added to other reaction wells not containing the molecule. To each reaction well 10 micro l of trimers formed from the synthetic peptide was added. After a sufficient time for the trimers to contact the molecule, 10 micro l of desired concentration of labeled **HR2** peptide was added to the reaction wells. The result indicated inhibition of binding interaction between **HR1** and **HR2** regions by the molecule. The molecule was then subjected to in vitro infectivity assay against HIV-1. The IC50 of the molecule was found to be 0.002 micro g/ml.

USE - (M1) is useful for identifying a compound that inhibits transmission of HIV to a target cell (claimed). The synthetic peptide of (M1) is useful for producing antiviral agents having activity against HIV. The compound identified by (M1) is useful as an antiviral agent for HIV.

DESCRIPTION OF DRAWING(S) - The figure is a graph representing use of synthetic peptide and heptad repeat (**HR2**) peptide for producing molecule that inhibits binding between **HR1** and **HR2** sequences.

Dwg.5/5

L7 ANSWER 2 OF 2 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2004-316084 [29] WPIDS
DNC C2004-119901
TI New synthetic peptide comprising an amino acid sequence derived from the **HR1** region of HIV-1 gp41, useful for inhibiting transmission of HIV-1 to a cell.
DC B04 D16
IN DELMEDICO, M K; **DWYER, J**
PA (DELM-I) DELMEDICO M K; (DWYE-I) DWYER J; (TRIM-N) TRIMERIS INC
CYC 102
PI WO 2004029074 A2 20040408 (200429)* EN 94
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

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     US 2004076637   A1 20040422 (200429)
     AU 2003287011   A1 20040419 (200462)
     AU 2003287011   A8 20051103 (200629)
ADT  WO 2004029074 A2 WO 2003-US30286 20030926; US 2004076637 A1 Provisional US
     2002-414514P 20020927, US 2003-664021 20030916; AU 2003287011 A1 AU
     2003-287011 20030926; AU 2003287011 A8 AU 2003-287011 20030926
FDT  AU 2003287011 A1 Based on WO 2004029074; AU 2003287011 A8 Based on WO
     2004029074
PRAI US 2003-664021       20030916; US 2002-414514P      20020927
AB   WO2004029074 A UPAB: 20040505
     NOVELTY - A new synthetic peptide comprises an amino acid sequence derived
     from the HR1 region of HIV-1 gp41.
          DETAILED DESCRIPTION - A new synthetic peptide comprises an amino
     acid sequence derived from the HR1 region of HIV-1 gp41; where the HR1
     region consists of native 59-amino acid sequence or polymorphisms; where
     the HR1 region from which the synthetic peptide is derived comprises a
     hydrophobic domain of amino acids corresponding to amino acid residues in
     positions 28 to 36 of 59-amino acid sequence or its polymorphisms; where
     the amino acid residues comprising the hydrophobic domain correspond to
     heptad repeat positions efgabcdef; and where the amino acid sequence of
     the synthetic peptide further comprises one or more amino acid
     substitutions in the heptad repeat positions efgabcdef comprising the
     hydrophobic domain, as compared to the native amino acid sequence of the
     HR1 region, which enables synthetic peptide to self-assemble in solution
     into trimers.
          INDEPENDENT CLAIMS are also included for the following:
          (1) a trimer formed from synthetic peptide;
          (2) a method for inhibiting transmission of HIV-1 to a cell;
          (3) a method for inhibiting transmission of HIV-1 to a target cell;
     and
          (4) a method for inhibiting HIV fusion with a target cell.
          ACTIVITY - Anti-HIV. No biological data given.
          MECHANISM OF ACTION - Gene therapy.
          USE - The synthetic peptide is useful for inhibiting transmission of
     HIV-1 to a cell (claimed).
     Dwg.0/4


=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               31.94      40.86

FILE 'MEDLINE' ENTERED AT 02:58:37 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.
```

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> e delmedico m k/au
E1            1     DELMEDICO ANTONIETTA/AU
E2            1     DELMEDICO J/AU
E3            1 --> DELMEDICO M K/AU
E4            1     DELMEDICO MARY K/AU
E5            1     DELMEDICO P/AU
E6            1     DELMEDICO V J/AU
E7            1     DELMEE EVELYNE/AU
E8            1     DELMEE J/AU
E9           87     DELMEE M/AU
E10          15     DELMEE MICHEL/AU
E11           1     DELMEEE M/AU
E12           2     DELMEIRE D/AU

=> s e3 or e4
              1 "DELMEDICO M K"/AU
              1 "DELMEDICO MARY K"/AU
L8            2 "DELMEDICO M K"/AU OR "DELMEDICO MARY K"/AU

=> d l8,cbib,ab,1-2

L8   ANSWER 1 OF 2     MEDLINE on STN
2003199173.    PubMed ID: 12718536.   The hydrophobic pocket contributes to the
     structural stability of the N-terminal coiled coil of HIV gp41 but is not
     required for six-helix bundle formation. Dwyer John J; Hasan Aisha; Wilson
     Karen L; White Jonathan M; Matthews Thomas J; Delmedico Mary K.
     (Trimeris, Inc., 3518 Westgate Drive, Durham, North Carolina 27707, USA. )
     Biochemistry, (2003 May 6) Vol. 42, No. 17, pp. 4945-53.  Journal code:
     0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.
AB   In models of HIV fusion, the glycoprotein gp41 is thought to form a
     six-helix bundle during viral fusion with the target cell.  This bundle is
     comprised of three helical regions (from the heptad repeat 2, or HR2,
     region of gp41) bound to an inner, trimeric, coiled-coil core (from the
     HR1 region).  Although much has been learned about the structure and
     thermodynamics of this complex, the energetics of the isolated HR1
     self-associated oligomer remain largely unknown.  By systematically
     studying self-association through a series of truncations based on a
     51-mer HR1 peptide (T865), we have identified amino acid segments which
     contribute significantly to the stability of the oligomeric HR1 complex.
     Biophysical characterization of C-terminal truncations of T865 identifies
     a 10-15-amino acid region that is essential for HR1 oligomerization.  This
     region coincides with a hydrophobic pocket that provides important
     contacts for the interaction of HR2 helices.  Complete removal of this
     pocket abolishes HR1 oligomerization.  Despite the dramatic reduction in
     stability, the monomeric HR1 peptides are still able to form stable
     six-helix bundles in the presence of HR2 peptides.  Truncations on the
     N-terminal side of T865 have little effect on oligomerization but
     significantly reduce the stability of the HR1-HR2 six-helix bundle.
     Unlike the HR2 binding site, which extends along a hydrophobic groove on
     the HR1 oligomer, the residues that are critical for HR1 oligomerization
     are concentrated in a 10-15-amino acid region.  These results demonstrate
     that there are localizations of binding energy, or "hot spots", in the
     self-association of peptides derived from the HR1 region of gp41.

L8   ANSWER 2 OF 2     MEDLINE on STN
2001031173.    PubMed ID: 11038187.   Evidence that the transition of HIV-1
     gp41 into a six-helix bundle, not the bundle configuration, induces
     membrane fusion. Melikyan G B; Markosyan R M; Hemmati H; Delmedico M K;
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Lambert D M; Cohen F S. (Department of Molecular Biophysics and Physiology, Rush Medical College, Chicago, Illinois 60612, USA.) The Journal of cell biology, (2000 Oct 16) Vol. 151, No. 2, pp. 413-23. Journal code: 0375356. ISSN: 0021-9525. Pub. country: United States. Language: English.

AB Many viral fusion proteins exhibit a six-helix bundle as a core structure. HIV Env-induced fusion was studied to resolve whether membrane merger was due to the transition into the bundle configuration or occurred after bundle formation. Suboptimal temperature was used to arrest fusion at an intermediate stage. When bundle formation was prevented by adding inhibitory peptides at this stage, membranes did not merge upon raising temperature. Inversely, when membrane merger was prevented by incorporating lysophosphatidylcholine (LPC) into cell membranes at the intermediate, the bundle did not form upon optimizing temperature. In the absence of LPC, the six-helix bundle did not form when the temperature of the intermediate was raised for times too short to promote fusion. Kinetic measures showed that after the temperature pulse, cells had not advanced further toward fusion. The latter results indicate that bundle formation is the rate-limiting step between the arrested intermediate and fusion. Electrical measures showed that the HIV Env-induced pore is initially large and grows rapidly. It is proposed that bundle formation and fusion are each contingent on the other and that movement of Env during its transition into the six-helix bundle directly induces the lipid rearrangements of membrane fusion. Because peptide inhibition showed that, at the intermediate stage, the heptad repeats of gp41 have become stably exposed, creation of the intermediate could be of importance in drug and/or vaccine development.

```
=> d his

     (FILE 'HOME' ENTERED AT 02:53:18 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 02:55:22 ON 02 OCT 2006
                E DELMEDICO MARY KAY/IN
L1            1 S E3
                E DWYER JOHN/IN
L2           31 S E3-E11
L3            2 S L2 AND (HR1 OR HR2)
L4            1 S L3 NOT L1

     FILE 'WPIDS' ENTERED AT 02:57:20 ON 02 OCT 2006
                E DELMEDICO M K/IN
L5            4 S E3
                E DWYER JOHN/IN
                E DWYER J/IN
L6           13 S E3
L7            2 S L6 AND (HR1 OR HR2)

     FILE 'MEDLINE' ENTERED AT 02:58:37 ON 02 OCT 2006
                E DELMEDICO M K/AU
L8            2 S E3 OR E4

=> e dwyer john/au
E1          25     DWYER JOHANNA/AU
E2          25     DWYER JOHANNA T/AU
E3           5 --> DWYER JOHN/AU
E4           1     DWYER JOHN J/AU
E5          12     DWYER JOHN J M/AU
E6           4     DWYER JOHN M/AU
E7           2     DWYER JONATHAN/AU
E8           2     DWYER JOSEPH R/AU
```

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E9            1     DWYER JOYCE CAROL/AU
E10           2     DWYER JOYCE L/AU
E11           1     DWYER JOYCE LISA E A/AU
E12           4     DWYER JOYCE P/AU

=> s e3
L9            5 "DWYER JOHN"/AU

=> s l9 not l8
L10           5 L9 NOT L8

=> d l10,cbib,ab,1-5

L10  ANSWER 1 OF 5     MEDLINE on STN
2006540900.    PubMed ID: 16632188.   A Correlation of FTIR Spectra Derived
     from Prostate Cancer Biopsies with Gleason Grade and Tumour Stage. Gazi
     Ehsan; Baker Matthew; Dwyer John; Lockyer Nicholas P; Gardner Peter;
     Shanks Jonathan H; Reeve Roy S; Hart Claire A; Clarke Noel W; Brown
     Michael D. (School of Chemical Engineering and Analytical Science,
     University of Manchester, Manchester, UK; Paterson Institute for Cancer
     Research, University of Manchester, Wilmslow Road, Manchester, M20 4BX,
     UK. ) European urology, (2006 Oct) Vol. 50, No. 4, pp. 750-61.  Electronic
     Publication: 2006-03-31. Journal code: 7512719. ISSN: 0302-2838. Pub.
     country: Switzerland. Language: English.
AB   OBJECTIVES: We introduce biochemistry as a second dimension to Gleason
     grading, using Fourier transform infrared (FTIR) microspectroscopy.  For
     the first time, we correlate FTIR spectra derived from prostate cancer
     (pCA) tissue with Gleason score and the clinical stage of the tumour at
     time of biopsy.  METHODS: Serial sections from paraffin-embedded pCA
     tissue were collected.  One was stained with hematoxylin and eosin and
     Gleason scored; FTIR spectra were collected from malignant locations using
     a second unstained section.  FTIR spectra, representing different Gleason
     grades, were used to construct a diagnostic classifier for pCA using
     linear discriminant analysis (LDA).  This model was blind tested using 383
     IR spectra from 36 biopsies.  RESULTS: Using a three-band Gleason
     criteria, we obtained sensitivity of >/=70% for the FTIR-LDA model to
     predict Gleason <7,=7, and >7, with specificities of >/=81%.  Using a
     threshold of Gleason/FTIR-LDA score of >/=8, we obtained a sensitivity and
     specificity of 71% and 67%, respectively, for the correlation with
     metastatic tumours using the FTIR-LDA system and 85% and 63%,
     respectively, for the correlation of metastatic tumours using the Gleason
     system.  CONCLUSIONS: There is a correlation between tissue architecture
     using Gleason score with tissue biochemistry using FTIR-LDA.  Both systems
     are similar in their performance in predicting metastatic behaviour in
     tumours from individual patients.

L10  ANSWER 2 OF 5     MEDLINE on STN
2004581920.    PubMed ID: 15485365.   A response to the Australian Health Care
     Agreements series. Dwyer John. (University of NSW. ) Australian health
     review : a publication of the Australian Hospital Association, (2003) Vol.
     26, No. 1, pp. 9.  Journal code: 8214381. ISSN: 0156-5788. Pub. country:
     Australia. Language: English.

L10  ANSWER 3 OF 5     MEDLINE on STN
2004102414.    PubMed ID: 14992399.   The combined application of FTIR
     microspectroscopy and ToF-SIMS imaging in the study of prostate cancer.
     Gazi Ehsan; Dwyer John; Lockyer Nicholas; Gardner Peter; Vickerman John
     C; Miyan Jaleel; Hart Claire A; Brown Mick; Shanks Jonathan H; Clarke
     Noel. (Department of Chemistry, UMIST, Manchester, UK M60 1QD. ) Faraday
     discussions, (2004) Vol. 126, pp. 41-59; discussion 77-92.  Journal code:
     9212301. ISSN: 1359-6640. Pub. country: England: United Kingdom. Language:
     English.
```

AB At present. a prognosis for prostate cancer (CaP) is determined by its accurate assessment of disease grade and stage. Histopathological typing using the Gleason grading system is the most universally accepted approach for grading CaP and provides an indication as to the aggressiveness of the tumour at the time of presentation. However, this system is based upon a visual criterion of pattern recognition that is operator dependent and subject to intra- and inter-observer variability, which can result in inappropriate patient management. Thus, there is a need for a molecular based diagnostic technique to grade tissue samples in a reliable and reproducible manner. In this paper we report a prototype diagnostic classifier for Gleason graded CaP tissue, based upon the integration of FTIR microspectroscopy with linear discriminant analysis (LDA). Blind testing of this model demonstrates 80% agreement of FTIR-LDA grade to histology, for the specimens analysed. We also study the effects of connective tissue absorption upon the area ratio of peaks at A1030 cm(-1)/A1080(cm(-1) which we use as a criterion to biospectroscopically map and distinguish areas of benign from malignant tissue. In addition, imaging time-of-flight secondary ion mass spectrometry (ToF-SIMS) has been applied to study freeze-dried, freeze-fractured prostate cancer cells in vitro. Preliminary results demonstrate localisation of various species including K, Ca and Mg within the cytoplasm that are present at millimolar concentrations and vital to cell physiology. The soft ionisation technique employed also permits for molecular information to be obtained and this has been used to evaluate chemically, different fracture planes within the analysis area.

L10 ANSWER 4 OF 5 MEDLINE on STN

2002408645. PubMed ID: 12162296. War on the roads. This war is sapping NHS of resources and inflicting untold grief. **Dwyer John**. BMJ (Clinical research ed.), (2002 Aug 3) Vol. 325, No. 7358, pp. 277. Journal code: 8900488. E-ISSN: 1468-5833. Pub. country: England: United Kingdom. Language: English.

L10 ANSWER 5 OF 5 MEDLINE on STN

2002233694. PubMed ID: 11912463. Screening for Neisseria gonorrhoeae and Chlamydia trachomatis at entertainment venues among men who have sex with men. Debattista Joseph; Clementson Chris; Mason Drew; **Dwyer John**; Argent Shelly; Woodward Charlotte; Dean Judith; Buks Lorraine; Copley Mark; Hinwood Greg; Benfield Craig; Walton Paul. (Brisbane Sexual Health AIDS Service, The Prince Charles Hospital Health Service District, 484 Adelaide Street, Brisbane, Queensland 4000, Australia.. joedebat@powerup.com.au) . Sexually transmitted diseases, (2002 Apr) Vol. 29, No. 4, pp. 216-21. Journal code: 7705941. ISSN: 0148-5717. Pub. country: United States. Language: English.

AB BACKGROUND: To assess the prevalence and increase awareness of Neisseria gonorrhoeae and Chlamydia trachomatis infections among men who have sex with men, a screening program was conducted at three inner-city homosexual entertainment venues and one community function. STUDY DESIGN: Each venue was accessed twice over a 3-month period between March and June 2000. First-catch urine specimens were collected for analysis by polymerase chain reaction (PCR), and throat swabs were collected for culture and PCR. RESULTS: A total of 202 men were tested during the 7 screening nights, including 16 who were tested more than once. From the 186 men tested for the first time, 184 urine specimens were collected, of which 8 (4.3%; 95% CI, 1.9-7.8%) were PCR-positive for C trachomatis and 1 (0.5%; 95% CI, 0-2.1%) was PCR-positive for N gonorrhoeae. Of the 161 throat swabs collected, none were positive for C trachomatis or N gonorrhoeae. CONCLUSIONS: C trachomatis is a potentially significant pathogen in this population of urban homosexual men. Screening programs such as these are valuable as health-promotion exercises.

```
=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     2.22      43.08

FILE 'USPATFULL' ENTERED AT 02:59:36 ON 02 OCT 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2006 (20060928/PD)
FILE LAST UPDATED: 28 Sep 2006 (20060928/ED)
HIGHEST GRANTED PATENT NUMBER: US7114185
HIGHEST APPLICATION PUBLICATION NUMBER: US2006218687
CA INDEXING IS CURRENT THROUGH 28 Sep 2006 (20060928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2006 (20060928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006


=> s (HIV or human immunodeficiency virus)
         45383 HIV
        522505 HUMAN
         25660 IMMUNODEFICIENCY
        105701 VIRUS
         18282 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L11      47774 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l11 and (HR1 or HR2)
           521 HR1
           432 HR2
L12        136 L11 AND (HR1 OR HR2)

=> s l12 and (HR1/clm or HR2/clm)
            31 HR1/CLM
            25 HR2/CLM
L13          8 L12 AND (HR1/CLM OR HR2/CLM)

=> d his

     (FILE 'HOME' ENTERED AT 02:53:18 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 02:55:22 ON 02 OCT 2006
                E DELMEDICO MARY KAY/IN
L1            1 S E3
                E DWYER JOHN/IN
L2           31 S E3-E11
L3            2 S L2 AND (HR1 OR HR2)
L4            1 S L3 NOT L1

     FILE 'WPIDS' ENTERED AT 02:57:20 ON 02 OCT 2006
                E DELMEDICO M K/IN
L5            4 S E3
                E DWYER JOHN/IN
                E DWYER J/IN
L6           13 S E3
L7            2 S L6 AND (HR1 OR HR2)

     FILE 'MEDLINE' ENTERED AT 02:58:37 ON 02 OCT 2006
                E DELMEDICO M K/AU
L8            2 S E3 OR E4
                E DWYER JOHN/AU
L9            5 S E3
```

```
L10             5 S L9 NOT L8

     FILE 'USPATFULL' ENTERED AT 02:59:36 ON 02 OCT 2006
L11         47774 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12           136 S L11 AND (HR1 OR HR2)
L13             8 S L12 AND (HR1/CLM OR HR2/CLM)

=> s l13 not l1
L14             7 L13 NOT L1

=> d l14,cbib,clm1-7
'CLM1-7' IS NOT A VALID FORMAT FOR FILE 'USPATFULL'

The following are valid formats:

The default display format is STD.

ABS -------- AB
ALL -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
             RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
             DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
             INCLM, INCLS, NCL, NCLM, NCLS, IC, IPCI,
             IPCI-2, IPCR, EXF, ARTU
ALLG ------- ALL plus PAGE.DRAW
BIB -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD, RLI,
             PRAI, DT, FS, EXNAM, LREP, CLMN, ECL, DRWN, LN.CNT
BIB.EX ----- BIB for original and latest publication
BIBG ------- BIB plus PAGE.DRAW
BROWSE ----- See "HELP BROWSE" or "HELP DISPLAY BROWSE".  BROWSE must
             entered on the same line as DISPLAY, e.g., D BROWSE.
CAS -------- OS, CC, SX, ST, IT
CBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PRAI, DT, FS
DALL ------- ALL, delimited for post-processing
FP --------- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI, RLI,
             PRAI, IC, IPCI, IPCI-2, IPCR, INCL, INCLM, INCLS, NCL,
             NCLM, NCLS, EXF, REP, REN, ARTU, EXNAM, LREP,
             CLMN, DRWN, AB
FP.EX ------ FP for original and latest publication
FPALL ------ PI, TI, IN, INA, PA, PAA, PAT, PETRM, DCD, AI,
             RLI, PRAI, IC, IPCI, IPCI-2, IPCR, INCL, INCLM, INCLS, NCL, NCLM,
             NCLS, EXF, REP, REN, ARTU, EXNAM, LREP, CLMN, DRWN, AB,
             PARN, SUMM, DRWD, DETD, CLM
FPBIB ------ PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI,
             RLI, PRAI, REP, REN, EXNAM, LREP, CLM, CLMN, DRWN
FHITSTR ---- HIT RN, its text modification, its CA index name, and
             its structure diagram
FPG -------- FP plus PAGE.DRAW
GI --------- PN and page image numbers
HIT -------- All fields containing hit terms
HITRN ------ HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
             its structure diagram
IABS ------- ABS, indented with text labels
IALL ------- ALL, indented with text labels
IALLG ------ IALL plus PAGE.DRAW
IBIB ------- BIB, indented with text labels
IBIB.EX ---- IBIB for original and latest publication
IBIBG ------ IBIB plus PAGE.DRAW
IMAX ------- MAX, indented with text labels
IMAX.EX ---- IMAX for original and latest publication
IND -------- INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, IPCI, IPCI-2, IPCR,
             EXF, ARTU, OS, CC, SX, ST, IT
```

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IPC.TAB ---- IPC in tabular format
ISTD ------- STD, indented with text labels
KWIC ------- All hit terms plus 20 words on either side
MAX -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
             RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
             DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
             INCLM, INCLS, NCL, NCLM, NCLS, IC, IPCI, IPCI-2,
             IPCR, EXF, ARTU OS, CC, SX, ST, IT
MAX.EX ----- MAX for original and latest publication
OCC -------- List of display fields containing hit terms
SBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
             DT, FS, LN.CNT
STD -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
             DT, FS, LN.CNT, INCL, INCLM, INCLS, NCL, NCLM, NCLS,
             IC, IPCI, IPCI-2, IPCR, EXF (STD is the default)
STD.EX ----- STD for original and latest publication
TRIAL ------ AN, TI, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC,
             IPCI, IPCI-2, IPCR

SCAN ------- AN, TI, NCL, NCLM, NCLS, IC, IPCI, IPCI-2, IPCR(random display
             without answer number.  SCAN must be entered on the
             same line as DISPLAY, e.g., D SCAN)
ENTER DISPLAY FORMAT (STD):ti

L14  ANSWER 1 OF 7  USPATFULL on STN
TI     Multimerised HIV fusion inhibitors


=> d l14,cbib,clm,1-7

L14  ANSWER 1 OF 7  USPATFULL on STN
2005:233109 Multimerised HIV fusion inhibitors.
    Etzerodt, Michael, Hinnerup, DENMARK
    Borean Pharma A/S, Aarhus C, DENMARK (non-U.S. corporation)
    US 2005202043 A1 20050915
    APPLICATION: US 2005-64115  A1  20050223 (11)
    PRIORITY: DK 2004-283  20040223
    WO 2005-DK121  20050223
    US 2004-546200P  20040223 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A fusion protein exhibiting anti-viral activity comprising: (i) a
       first polypeptide representing the HR2 region of the ectodomain of the
       human immunodeficiency virus gp41 protein or a part thereof, and
       (ii) a second polypeptide representing a multimerisation domain peptide.

       2. A fusion protein according to claim 1, wherein the multimerisation
       domain peptide is selected from the group consisting of a dimerising
       domain, a trimerising domain, a tetramerising domain, a pentamerising
       domain and a hexamerising domain.

       3. A fusion protein according to claim 1, wherein said first polypeptide
       is linked to the N-terminal amino acid residue of the multimerisation
       domain peptide.

       4. A fusion protein according to claim 1, wherein said first polypeptide
       is linked to the C-terminal amino acid residue of the multimerisation
       domain peptide.

       5. A fusion protein according to claim 1, wherein the multimerisation
       domain is a trimerising domain derived from tetranectin.
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6. A fusion protein according to claim 5, wherein the trimerising domain derived from tetranectin comprises a sequence having at least 68% amino acid sequence identity with the sequence of SEQ ID NO 2.

7. A fusion protein according to claim 5, wherein the amino acid sequence identity is at least 75%.

8. A fusion protein according to claim 5, wherein the trimerising domain derived from tetranectin comprises the amino acid sequence SEQ ID NO 2.

9. A fusion protein according to claim 5, wherein the trimerising domain derived from tetranectin comprises an amino acid sequence selected from the group consisting of SEQ ID NO 50, SEQ ID NO 51, SEQ ID NO 52, SEQ ID NO 53, SEQ ID NO 54, SEQ ID NO 55, SEQ ID NO 56, SEQ ID NO 57, SEQ ID NO 58, SEQ ID NO 59, SEQ ID NO 60, SEQ ID NO 61, SEQ ID NO 62, SEQ ID NO 63, SEQ ID NO 64, SEQ ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, SEQ ID NO 70, SEQ ID NO 71, SEQ ID NO 72 and SEQ ID NO 73.

10. A fusion protein according to claim 1, wherein the first polypeptide representing the **HR2** domain comprises the amino acid sequence of SEQ ID NO 1.

11. A fusion protein according to claim 1, wherein the first polypeptide representing the **HR2** region comprises a fragment of the amino acid sequence of SEQ ID NO 1.

12. A fusion protein according to claim 11, wherein the number of amino acids in said fragment is in a range selected from the group consisting of 20-73 amino acids, 30-73 amino acids, 40-70 amino acids, 30-65 amino acids, 30-60 amino acids, 30-55 amino acids, 30-50 amino acids, 30-45 amino acids, 30-40 amino acids and 30-35 amino acids.

13. A fusion protein according to claim 11, wherein the fragment of SEQ ID NO 1 comprises SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 49 or SEQ ID NO 159.

14. A fusion protein according to claim 11, wherein the fragment of SEQ ID NO 1 is selected from the group consisting of SEQ ID Nos 74-115.

15. A fusion protein according to claim 11, wherein the fragment of SEQ ID NO 1 is selected from the group consisting of SEQ ID Nos 116-158.

16. A fusion protein according to claim 1, wherein the first polypeptide representing the **HR2** domain comprises of an amino acid sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8 and SEQ ID NO 9.

17. A fusion protein according to claim 1, wherein the **human immunodeficiency virus** is selected from the group consisting of **HIV-1** and **HIV-2**.

18. A fusion protein according to claim 5, selected from the group consisting of BPFI-0100 (SEQ ID NO 10), BPFI-0200 (SEQ ID NO 11), BPFI-0300 (SEQ ID NO 12), BPFI-0101 (SEQ ID NO 42), BPFI-0201 (SEQ ID NO 43) and BPFI-0301 (SEQ ID NO 44).

19. A fusion protein according to claim 1, further comprising a linker between the first polypeptide and the second polypeptide.

20. A polypeptide complex comprising at least two fusion proteins

according to claim 1.

21. A polypeptide complex comprising three fusion proteins according to claim 1.

22. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-500 nM.

23. A method of treating **HIV** infection in a subject, comprising administering to the subject a therapeutically effective amount of the polypeptide complex according to claim 20 or 21.

24. A method according to claim 23, further comprising the administration of at least one further therapeutic agent.

25. A pharmaceutical composition comprising the fusion protein according to any of claims 1-19.

26. A method of producing a polypeptide complex according to claim 20 or 21, said method comprising the steps of (i) expressing or synthesizing a fusion protein exhibiting anti-viral activity, wherein said fusion protein comprises (a) a first polypeptide representing the **HR2** region of the ectodomain of the **human immunodeficiency virus** gp41 protein or a part thereof, and (b) a second polypeptide representing a multimerisation domain peptide, (ii) effecting complex formation between said fusion proteins and, (iii) isolating the resulting polypeptide complex and optionally subjecting said polypeptide complex to further processing.

27. A method according to claim 26, wherein the fusion protein comprises a third fusion partner.

28. A method according to claim 27, wherein the third fusion partner is ubiquitin.

29. A method according to claim 27, wherein the junction region between said third fusion partner and the fusion protein comprises a Granzyme B protease cleavage site.

30. A method of inhibiting human and non-human retroviral transmission to uninfected cells comprising administering the fusion protein according to any of claims 1-19 to a subject in need thereof.

31. A method of preparing a pharmaceutical composition comprising associating the fusion protein according to any of claims 1-19 with a pharmaceutically acceptable carrier.

32. A composition comprising a fusion protein according to any of claims 1-19.

33. An isolated nucleic acid sequence encoding the fusion protein according to any of claims 1-19.

34. A recombinant vector comprising the isolated nucleic acid sequence according to claim 33.

35. A host cell transformed with a vector according to claim 34.

36. A fusion protein according to claim 5, wherein the amino acid sequence identity is at least 87%.

37. A fusion protein according to claim 5, wherein the amino acid sequence identity is at least 92%.

38. A polypeptide complex comprising at least three fusion proteins according to claim 1.

39. A polypeptide complex comprising at least four fusion proteins according claim 1.

40. A polypeptide complex comprising at least five fusion proteins according to claim 1.

41. A polypeptide complex comprising at least six fusion proteins according to claim 1.

42. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-400 nM.

43. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-300 nM.

44. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-200 nM.

45. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-100 nM.

46. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-50 nM.

47. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-40 nM.

48. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-30 nM.

49. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-20 nM.

50. A polypeptide complex according to claim 20 or 21, exhibiting an in-vitro antiviral activity against strain IIIB of **HIV**-1 using MT4 cells as target cells, with an 50% inhibitory concentration (IC50) in the range of 1-10 nM.

51. A pharmaceutical composition comprising the polypeptide complex

according to claim 20 or 21.

52. A composition comprising a polypeptide complex according to claim 20 or 21.

53. A method of inhibiting human and non-human retroviral transmission to uninfected cells comprising administering the polypeptide complex according to claim 20 or 21 to a subject in need thereof.

54. A method of preparing a pharmaceutical composition comprising associating the polypeptide complex according to claim 20 or 21 with a pharmaceutically acceptable carrier.

L14 ANSWER 2 OF 7 USPATFULL on STN
2005:214901 Corona-virus-like particles comprising functionally deleted genomes

Rottier, Petrus Josephus Marie, Groenkan, NETHERLANDS
Bosch, Berend Jan, Utrecht, NETHERLANDS
US 2005186575 A1 20050825
APPLICATION: US 2003-750411 A1 20031230 (10)
PRIORITY: EP 2001-201861 20010517
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for at least in part inhibiting anti-parallel coiled coil formation of a coronavirus spike protein of a coronavirus, said method comprising: decreasing contact between heptad repeat regions of said coronavirus spike protein.

2. The method according to claim 1 wherein a peptide and/or a functional fragment and/or an equivalent thereof decreases contact between heptad repeat regions of said coronavirus spike protein.

3. The method according to claim 2 wherein the peptide and/or a functional fragment and/or an equivalent thereof comprises a heptad repeat region of a coronavirus spike protein.

4. The method according to claim 1, claim 2, or claim 3, wherein said heptad repeat region comprises an amino acid sequence of SARS **HR2** and/or **HR1** according to FIG. 1 (SEQ ID NOS: 23 118, respectively), and/or a functional fragment and/or a derivative thereof.

5. The method according to claim 1, wherein an antibody and/or a functional fragment and/or an equivalent thereof decreases contact between heptad repeat regions of said coronavirus spike protein.

6. The method according to claim 1, claim 2, claim 3, claim 4, or claim 5, wherein the coronavirus comprises a group 1 coronavirus.

7. The method according to claim 6, wherein the coronavirus comprises a feline corona virus.

8. The method according to claim 7, wherein the coronavirus comprises a feline infectious peritonitis (FIP) virus.

9. The method according to claim 6, wherein the coronavirus comprises a human corona virus.

10. The method according to claim 1, claim 2, claim 3, claim 4, or claim 5, wherein the coronavirus comprises a group 2 coronavirus.

11. The method according to claim 10, wherein said coronavirus comprises a mouse hepatitis virus (MHV).

12. A method according to claim 1, claim 2, claim 3, claim 4, or claim 5, wherein the coronavirus causes Severe Acute Respiratory Syndrome (SARS).

13. A method for inhibiting of coronavirus spike protein mediated cell to cell fusion, said method comprising: decreasing contact between heptad repeat regions of said coronavirus spike protein.

14. A method of selecting a compound that binds to a heptad repeat region of a coronavirus spike protein, said method comprising: contacting in vitro at least one heptad region of a coronavirus spike protein with a collection of compounds, and measuring the formation of an anti-parallel coiled coil in said coronavirus spike protein.

15. A compound selected by the method of claim 14.

16. An antibody, functional fragment, and/or derivative thereof, said antibody, functional fragment, and/or derivative thereof capable of decreasing the contact between heptad repeat regions of a coronavirus spike protein.

17. A composition comprising: the compound of claim 15, and/or an antibody and/or a functional fragment and/or a derivative thereof, capable of decreasing the contact between heptad repeat regions of a coronavirus spike protein, and a suitable diluent and/or carrier.

18. A method of treating coronavirus infections in a subject, said method comprising: providing to the subject the composition of claim 17.

19. A diagnostic kit for detecting coronavirus infection in a sample of a subject, said diagnostic kit comprising: the compound of claim 15 or an antibody, functional fragment, and/or derivative thereof, said antibody, functional fragment, and/or derivative thereof capable of decreasing the contact between heptad repeat regions of a coronavirus spike protein, together with means of detecting binding of said compound or antibody functional fragment, and/or derivative thereof to the coronavirus.

20. A diagnostic kit for detecting antibodies directed against coronavirus in a sample from a subject, said diagnostic kit comprising: the compound according to claim 15, and means for detecting binding of said compound to said antibodies.

21. A method of attenuating a coronavirus, said method comprising: decreasing the contact between heptad repeat regions of the spike protein of said coronavirus.

22. An attenuated coronavirus having decreased contact between heptad repeat regions of the spike protein of said attenuated coronavirus.

23. The method according to claim 3 wherein said peptide comprises an amino acid sequence according to peptide sHR2-1, and/or sHR2-2, and/or sHR2-8, and/or sHR2-9 as depicted in FIG. 11B, and/or a functional fragment and/or an equivalent thereof.

24. A method for at least in part inhibiting a fusion of a coronavirus with a cell membrane, said method comprising decreasing binding of a fusion peptide with said cell membrane.

25. The method according to claim 24, wherein said fusion peptide comprises the amino acid sequence of SARS-CoV as depicted in FIG. 17.

26. The method according to claim 24, wherein a specific binding molecule for said fusion peptide decreases binding of a fusion peptide with said cell membrane.

27. The method according to claim 26, wherein said specific binding molecule is an antibody, functional fragment thereof, and/or derivative thereof.

L14 ANSWER 3 OF 7 USPATFULL on STN
2004:292181 Amino-modified polysaccharides and methods of generating and using same.
Lapidot, Aviva, Rehovot, ISRAEL
Vijayabaskar, Veerappan, Tamil Nadu, INDIA
Borkow, Gadi, Kfar Gibton, ISRAEL
US 2004229265 A1 20041118
APPLICATION: US 2004-831224 A1 20040426 (10)
PRIORITY: US 2003-465775P 20030428 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A pharmaceutical composition comprising, as an active ingredient, an amino-modified polysaccharide having at least one amino group linked to a peptide composed of at least two basic amino acid residues.

2. The pharmaceutical composition of claim 1, wherein said at least one amino group is an alkyl amino group.

3. The pharmaceutical composition of claim 2, wherein said alkyl amino group is linked to a first saccharide unit of said polysaccharide.

4. The pharmaceutical composition of claim 1, wherein said amino-modified polysaccharide is an aminoglycoside antibiotic.

5. The pharmaceutical composition of claim 4, wherein said aminoglycoside antibiotic is selected from the group consisting of neomycin, kanamycin, sisomycin, fortimycin, paromomycin, neamine and gentamycin.

6. The pharmaceutical composition of claim 1, wherein said basic amino acid residues are selected from the group consisting of arginines, lysines, histidines and combinations thereof.

7. The pharmaceutical composition of claim 1, wherein said peptide is further composed of glutamine and/or aspargine.

8. A pentaargininamido-paromomycin conjugate (ParomR5).

9. An argininamido-paramomycin conjugate (ParomR1) of a formula: ##STR6##

10. A tetraargininamido-neamine conjugate.

11. An argininamido-neamine conjugate (NeamR1) of a formula: ##STR7##

12. A diargininamido-neomycin B conjugate (NeoR2) of a formula: ##STR8##

13. An argininamido-neomycin B conjugate (NeoR1) of a formula: ##STR9##

14. An argininamido-neomycin B conjugate (NeoR1) of a formula: ##STR10##

15. A method of selectively protecting an alkyl amino group of a polyamino cyclic compound, the method comprising attaching an N-protecting group to the alkyl amino group of the polyamino cyclic compound, said N-- protecting group having a size selected suitable for selectively reacting with the alkyl amino group, to thereby selectively protect the alkyl amino group of the polyamino cyclic compound.

16. The method of claim 15, further comprising protecting non-amine reactive groups of the polyamino cyclic compounds prior to said attaching said N-protecting group.

17. The method of claim 15, wherein said N-protecting group is a trityl halide.

18. The method of claim 17, wherein said trytil halide is trityl chloride.

19. A method of generating a saccharide-chemical moeity site specific conjugate, the method comprising: (a) providing a saccharide having a reactive alkyl amino group and protected non-alkyl amino reactive groups and; (b) reacting said saccharide with a chemical moiety, thereby generating the saccharide-chemical moeity site specific conjugate.

20. The method of claim 19, wherein said saccharide is a mono-saccharide or an oligo-saccharide.

21. The method of claim 19, wherein said saccharide is an aminoglycoside antibiotic selected from the group consisting of neomycin, kanamycin, sisomycin, fortimycin, paromomycin, neamine and gentamycin.

22. The method of claim 19, wherein said moiety is an amino acid.

23. The method of claim 19, wherein said moiety is a cross linker.

24. A method of identifying a potent anti **HIV** agent, the method comprising: (a) providing a plurality of putative anti **HIV** agents, and; (b) identifying an anti **HIV** agent of said plurality of putative anti **HIV** agents incapable of inducing mutational instability in a predetermined sequence region of gp120, gp41 and/or CXCR4 thereby identifying the potent anti **HIV** agent.

25. The method of claim 24, wherein said sequence region is a nucleic acid sequence.

26. The method of claim 24, wherein said sequence region is an amino acid sequence.

27. The method of claim 24, wherein said identifying said anti **HIV** agent incapable of inducing said mutational instability in said predetermined sequence region of gp120, gp41 and/or CXCR4 is effected in a cell culture being infected with an **HIV** virus.

28. The method of claim 24, wherein said predetermined sequence region of gp120 is selected from the group consisting of C3, C4, V1, V2, V2, V3 and V4.

29. The method of claim 24, wherein said predetermined sequence region of gp41 is selected from the group consisting of **HR1** and **HR2**.

30. A method of generating an oligo-saccharide, the method comprising: (a) providing at least two saccharides each having at least one reactive alkyl amino group and protected non-alkyl amino reactive groups; and (b) reacting said at least two saccharides, thereby generating the oligo-saccharide.

31. The method of claim 30, wherein said reacting said at least two saccharides is effected via a linker.

32. The method of claim 30, wherein each of said at least two saccharides is a mono saccharide or an oligosaccharide and wherease at least one saccharide unit in said oligo saccharide.

33. A method of treating a viral infection in a subject, the method comprising providing to a subject in need thereof a pharmaceutical composition including an amino-modified polysaccharide having at least one amino group linked to a peptide composed of at least two basic amino acid residues.

34. The method composition of claim 33, wherein said at least one amino group is an alkyl amino group.

35. The method of claim 34, wherein said alkyl amino group is linked to a first saccharide unit of said polysaccharide.

36. The method of claim 33, wherein said amino-modified polysaccharide is an aminoglycoside antibiotic.

37. The method of claim 36, wherein said aminoglycoside antibiotic is selected from the group consisting of neomycin, kanamycin, sisomycin, fortimycin, paromomycin, neamine and gentamycin.

38. The method of claim 33, wherein said basic amino acid residues are selected from the group consisting of arginines, lysines, histidines and combinations thereof.

L14 ANSWER 4 OF 7 USPATFULL on STN
2004:159410 Conjugates comprised of polymer and **HIV** gp41-derived peptides and their use in therapy.
Bray, Brian, Graham, NC, UNITED STATES
Kang, Myung-Chol, Chapel Hill, NC, UNITED STATES
Tvermoes, Nicolai, Durham, NC, UNITED STATES
Kinder, Daniel, Durham, NC, UNITED STATES
Lackey, John William, Hillsborough, NC, UNITED STATES
US 2004122214 A1 20040624
APPLICATION: US 2003-671282 A1 20030924 (10)
PRIORITY: US 2002-414439P 20020927 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A conjugate comprising a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a heptad repeat region of **Human Immunodeficiency Virus** (**HIV**) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the conjugate has

durability comprising antiviral activity against **HIV** strains resistant to synthetic peptide alone.

2. The conjugate according to claim 1, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

3. The conjugate according to claim 2, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

4. The conjugate according to claim 1, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41.

5. The conjugate according to claim 4, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

6. The conjugate according to claim 1, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

7. The conjugate according to claim 6, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

8. The conjugate according to claim 1, wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41, and wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

9. The conjugate according to claim 1, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

10. A method of making a conjugate, the method comprising the steps of: (a) reacting a first molecule of synthetic peptide with a polymer in forming an intermediate comprising a first intermediate, wherein the first molecule of synthetic peptide operably binds to a first reactive functionality of the polymer; and (b) reacting the intermediate comprising the first intermediate with a second molecule of synthetic peptide, wherein the second molecule of synthetic peptide operably binds to the intermediate comprising the first intermediate via a second reactive functionality of the polymer, in forming a conjugate comprised of a polymer to which is operably bound no less than two molecules of synthetic peptides; and wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a heptad repeat region of **Human Immunodeficiency Virus** (**HIV**) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the conjugate has durability comprising antiviral activity against **HIV** strains resistant to synthetic peptide alone.

11. The method according to claim 10, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

12. The method according to claim 11, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

13. The method according to claim 10, wherein each synthetic peptide of

the conjugate comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41.

14. The method according to claim 13, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

15. The method according to claim 10, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

16. The method according to claim 15, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

17. The method according to claim 10, wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41, and wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

18. The method according to claim 10, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

19. A method of inhibiting transmission of **HIV** to a target cell, the method comprising adding to the virus and the cell an amount of conjugate effective to inhibit infection of the cell by the virus; wherein the conjugate comprises a polymer to which is operably bound no less than two molecules of synthetic peptides, wherein each molecule of synthetic peptide is operably bound to the polymer via a reactive functionality, wherein each synthetic peptide comprises an amino acid sequence derived from a heptad repeat region of **Human Immunodeficiency Virus** (**HIV**) gp41, wherein synthetic peptide comprises an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acids, and wherein the conjugate has durability comprising antiviral activity against **HIV** strains resistant to synthetic peptide alone.

20. The method according to claim 19, wherein the polymer comprises a molecular weight in a range of molecular weights of from about 200 daltons to about 20,000 daltons.

21. The method according to claim 20, wherein the polymer comprises polyethylene glycol comprising a specific number of ethylene units.

22. The method according to claim 19, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41.

23. The method according to claim 22, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

24. The method according to claim 19, wherein each synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

25. The method according to claim 24, wherein each synthetic peptide of the conjugate comprises an identical amino acid sequence.

26. The method according to claim 19, wherein at least one molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR1** region of **HIV** gp41, and wherein at least one

molecule of synthetic peptide of the conjugate comprises an amino acid sequence derived from the **HR2** region of **HIV** gp41.

27. The method according to claim 19, wherein the molecules of synthetic peptide are operably bound to the polymer via a portion of each synthetic peptide selected from the group consisting of an N-terminus, a C-terminus, and an internal lysine.

28. The method according to claim 19, wherein the conjugate inhibits fusion between the virus and the target cell in inhibiting infection of the cell by the virus.

29. The method according to claim 19, wherein the conjugate further comprises a pharmaceutically acceptable carrier.

30. The method according to claim 29, wherein the conjugate is administered to an **HIV**-infected individual.

L14 ANSWER 5 OF 7 USPATFULL on STN
2004:120446 Method for production of antivirals by use of **HIV**-derived **HR1** peptides, and trimers formed therefrom.
Dwyer, John, Chapel Hill, NC, UNITED STATES
Delmedico, Mary K., Raleigh, NC, UNITED STATES
US 2004091855 A1 20040513
APPLICATION: US 2003-671316 A1 20030924 (10)
PRIORITY: US 2002-414515P 20020927 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for identifying a compound that inhibits transmission of **HIV** to a target cell, the method comprising contacting synthetic peptide comprising trimers in the presence of a compound and with **HR2** peptide under conditions and for a time sufficient to allow formation of a complex between the synthetic peptide comprising trimers and **HR2** peptide in vitro; and detecting the amount of complex formed; wherein inhibition or reduction of complex formation in the presence of the compound, as compared to complex formation in the absence of the compound, is indicative of ability of the compound to inhibit transmission of **HIV** to a target cell; and wherein synthetic peptide comprises an amino acid sequence derived from the **HR1** region of **HIV**-1 gp41; wherein the **HR1** region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; wherein the **HR1** region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids corresponding to amino acid residues in positions 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and wherein the amino acid sequence of the synthetic peptide further comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the **HR1** region, which enables synthetic peptide to self-assemble in solution into trimers.

2. The method according to claim 1, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising either a substitution in the "c" position, or a substitution in both the "g" position and the "c" position, of the heptad repeat positions "efgabcdef".

3. The method according to claim 2, wherein the synthetic peptide comprises an amino acid substitution additional to a substitution in

either the "c" position or both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

4. The method according to claim 1, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" that are in a position of the heptad repeat positions selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

5. The method according to claim 4, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

6. The method according to claim 1, wherein the synthetic peptide further comprises a component selected from the group consisting of one or more reactive functionalities, a macromolecular carrier, a pharmaceutically acceptable carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

7. The method according to claim 1, wherein the synthetic peptide is predominately in trimeric form.

8. The method according to claim 1, wherein the synthetic peptide is in a monomer-trimer equilibrium.

9. A method for producing a drug that inhibits transmission of **HIV** to a target cell, the method comprising contacting synthetic peptide comprising trimers in the presence of a compound and with **HR2** peptide under conditions and for a time sufficient to allow formation of a complex between the synthetic peptide comprising trimers and **HR2** peptide in vitro; and detecting the amount of complex formed; wherein inhibition or reduction of complex formation in the presence of the compound is indicative of ability of the compound to inhibit transmission of **HIV** to a target cell; and wherein the drug comprises the compound contacted with a pharmaceutically acceptable carrier in producing the drug; and wherein synthetic peptide comprises an amino acid sequence derived from the **HR1** region of **HIV-1** gp41; wherein the **HR1** region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; wherein the **HR1** region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids corresponding to amino acid residues in positions 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and wherein the amino acid sequence of the synthetic peptide further comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the **HR1** region, which enables synthetic peptide to self-assemble in solution into trimers.

10. The method according to claim 9, wherein the amino acid sequence of

the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising either a substitution in the "c" position, or a substitution in both the "g" position and the "c" position, of the heptad repeat positions "efgabcdef".

11. The method according to claim 10, wherein the synthetic peptide comprises an amino acid substitution additional to a substitution in either the "c" position or both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

12. The method according to claim 9, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" that are in a position of the heptad repeat positions selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

13. The method according to claim 12, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

14. The method according to claim 9, wherein the synthetic peptide further comprising a component selected from the group consisting of one or more reactive functionalities, a macromolecular carrier, a pharmaceutically acceptable carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

15. The method according to claim 9, wherein the synthetic peptide is predominately in trimeric form.

16. The method according to claim 9, wherein the synthetic peptide is in a monomer-trimer equilibrium.

17. In a method for identifying or producing a molecule that can inhibit the binding between **HR1** and **HR2** regions of **HIV** gp41, the improvement which comprises: use of a trimer as a binding partner with **HR2** peptide in detecting in vitro the ability of the molecule to bind to an HR (heptad repeat) region of **HIV** gp41; wherein the trimer is comprised of synthetic peptide comprising an amino acid sequence derived from the **HR1** region of **HIV**-1 gp41; wherein the **HR1** region consists of native amino acid sequence shown as SEQ ID NO:1 or polymorphisms thereof; wherein the **HR1** region from which the synthetic peptide is derived comprises a hydrophobic domain of amino acids corresponding to amino acid residues in positions 28 to 36 of SEQ ID NO:1 or polymorphisms thereof; wherein the amino acid residues comprising the hydrophobic domain correspond to heptad repeat positions "efgabcdef"; and wherein the amino acid sequence of the synthetic peptide further comprises one or more amino acid substitutions in the heptad repeat positions "efgabcdef" comprising the hydrophobic domain, as compared to the native amino acid sequence of the **HR1** region, which enables synthetic peptide to self-assemble in solution into trimers.

18. The method according to claim 17, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising either a substitution in the "c" position, or a substitution in both the "g" position and the "c" position, of the heptad repeat positions "efgabcdef".

19. The method according to claim 18, wherein the synthetic peptide comprises an amino acid substitution additional to a substitution in either the "c" position or both the "g" position and "c" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of an "a" position, a "d" position, a "b" position, and a combination thereof.

20. The method according to claim 17, wherein the amino acid sequence of the synthetic peptide comprises one or more amino acid substitutions in the hydrophobic domain comprising the heptad repeat positions "efgabcdef" that are in a position of the heptad repeat positions selected from the group consisting of a C-terminal "e" position, a C-terminal "f" position, and a combination thereof.

21. The method according to claim 20, wherein the synthetic peptide comprises an amino acid substitution additional to the substitution in one or more of the "e" position and the "f" position, wherein the additional amino acid substitution is in one or more amino acid positions of one or more heptads of the synthetic peptide, and wherein the one or more amino acid positions is selected from the group consisting of the "a" position, a "d" position, a "b" position, and a combination thereof.

22. The method according to claim 17, wherein the synthetic peptide further comprising a component selected from the group consisting of one or more reactive functionalities, a macromolecular carrier, a pharmaceutically acceptable carrier, an amino acid substitution comprising an addition of no less than one amino acid and no more than twenty amino acids to either or both of the amino terminus or carboxy terminus of the synthetic peptide, and a combination thereof.

L14 ANSWER 6 OF 7 USPATFULL on STN
2004:94257 Corona-virus-like particles comprising functionally deleted genomes.
Rottier, Petrus Josephus Marie, Groenekan, NETHERLANDS
Bosch, Berend-Jan, Utrecht, NETHERLANDS
US 2004071709 A1 20040415
APPLICATION: US 2003-414256 A1 20030414 (10)
PRIORITY: EP 2001-201861 20010517
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for at least in part inhibiting anti-parallel coiled coil formation of a coronavirus spike protein, said method comprising: decreasing the contact between heptad repeat regions of the coronavirus spike protein.

2. The method according to claim 1 wherein said decrease is provided by a peptide and/or a functional fragment and/or an equivalent thereof.

3. The method according to claim 2 wherein said decrease is provided by a peptide comprising a heptad repeat region of a corona viral spike protein and/or a functional fragment and/or an equivalent thereof.

4. The method according to any of claims 1-3, wherein said heptad repeat region comprises an amino acid sequence of SARS **HR2** according to FIG. 9, and/or a functional fragment and/or an equivalent thereof.

5. The method according to claim 1, wherein said decrease is provided by an antibody and/or a functional fragment and/or an equivalent thereof.

6. The method according to any of claims 1-5, wherein said coronavirus is a group 1 coronavirus.

7. The method according to claim 6, wherein said coronavirus is a feline coronavirus.

8. The method according to claim 7, wherein said feline coronavirus is feline infectious peritonitis (FIP) virus.

9. The method according to claim 6, wherein said coronavirus comprises a human corona virus.

10. The method according to any of claims 1-5, wherein said coronavirus comprises a group 2 coronavirus.

11. The method according to claim 10, wherein said coronavirus comprises a mouse hepatitis virus (MHV).

12. The method according to any of claims 1-5, wherein said coronavirus causes Severe Acute Respiratory Syndrome (SARS).

13. A method for inhibiting coronavirus spike protein mediated cell to cell fusion, said method comprising: decreasing the contact between said spike protein's heptad repeat regions.

14. A method of selecting a binding compound to a heptad repeat region of a coronavirus spike protein, said method comprising: contacting in vitro at least one heptad region of a coronavirus spike protein with a collection of compounds and measuring the formation of an anti-parallel coiled coil in said protein.

15. A binding compound selected by the method according to claim 14.

16. An antibody or a functional fragment and/or equivalent thereof, said antibody or functional fragment and/or equivalent thereof capable of decreasing the contact between heptad repeat regions of a coronavirus spike protein.

17. A pharmaceutical composition comprising: the binding compound of claim 15, and/or an antibody or functional fragment and/or equivalent thereof capable of decreasing the contact between heptad repeat regions of a coronavirus spike protein, and a suitable diluent and/or carrier.

18. A method of treating coronavirus infections, said method comprising: providing to a subject the pharmaceutical: composition of claim 17.

19. A diagnostic kit for detecting coronavirus infection in a sample taken from a subject, said diagnostic kit comprising: the binding compound of claim 15 or an antibody or functional fragment and/or equivalent thereof capable of decreasing the contact between heptad repeat regions of a coronavirus spike protein, and means for detecting binding of said compound or antibody to said coronavirus.

20. A diagnostic kit for detecting coronavirus antibodies in a sample

taken from a subject, said diagnostic kit comprising: the binding compound of claim 15, and means for detecting binding of said compound to said antibodies.

21. A method of attenuating a coronavirus, said method comprising: decreasing the contact between heptad repeat regions of the spike protein of said coronavirus.

22. An attenuated coronavirus characterized in that the contact between heptad repeat regions of the spike protein of said coronavirus is decreased.

L14 ANSWER 7 OF 7 USPATFULL on STN
2003:112907 Ribozyme mediated inactivation of the androgen receptor.
Roy, Arun K., San Antonio, TX, UNITED STATES
Chen, Shuo, San Antonio, TX, UNITED STATES
Board of Regents, The University of Texas System (U.S. corporation)
US 2003077639 A1 20030424
APPLICATION: US 2002-246078 A1 20020917 (10)
PRIORITY: US 1996-16590P 19960508 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A synthetic ribozyme capable of selectively targeting androgen receptor mRNA.

2. The synthetic ribozyme of claim 1 further described as a hammerhead ribozyme.

3. The synthetic ribozyme of claim 2 further defined as cleaving human androgen receptor mRNA.

4. The synthetic ribozyme of claim 1 having a sequence as defined in SEQ ID NO: 9.

5. The synthetic ribozyme of claim 1 further defined as HR-2.

6. A gene encoding the synthetic ribozyme of claim 1.

7. A vector comprising the gene of claim 5, wherein the expression of said gene in a human prostatic cancer cell is capable of inhibiting androgen receptor activation.

8. The vector of claim 7 further defined as comprising a prostate tissue specific promoter.

9. The vector of claim 7 wherein the prostate tissue specific promoter is an RNA polymerase II promoter or an RNA polymerase III promoter.

10. The vector of claim 9 wherein the RNA polymerase II promoter is a prostate specific antigen promoter sequence or a probasin promoter sequence.

11. The vector of claim 9 wherein the RNA polymerase II promoter is derived from a small nuclear RNA (U6 RNA) sequence.

12. The vector of claim 7 further defined as a U6-**HR2**, U6-mut **HR2** or U6-anti-**HR2** construct.

13. A method for reducing androgen receptor activity in an animal having prostate hyperplasia comprising: administering a pharmacologically

active preparation comprising the vector of claim 7.

14. A method for treating prostate hyperplasia comprising: administering to a patient in need thereof a pharmaceutically acceptable formulation of a pharmacologically active preparation of a ribozyme gene construct, comprising a human promoter sequence in a suitable vector carrier, wherein said ribozyme gene construct comprises a ribozyme gene that provides an expression product capable of selectively reducing androgen receptor activation.

15. The method of claim 14 wherein the ribozyme gene construct comprises an HR-2 ribozyme gene.

16. The method of claim 14 wherein the HR-2 ribozyme gene has a sequence of SEQ. ID NO: 9.

17. The method of claim 14 wherein the human promoter sequence is a human prostate specific antigen sequence.

18. The method of claim 17 wherein the human prostate specific antigen sequence has a sequence of Gen Bank Accession No: U37672.

```
=> file wpids
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               16.86      59.94

FILE 'WPIDS' ENTERED AT 03:00:38 ON 02 OCT 2006
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MOST RECENT DERWENT UPDATE:     200662        <200662/DW>
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    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

=> s (HIV or human immunodeficiency virus)
         22722 HIV
        185899 HUMAN
          8060 IMMUNODEFICIENCY
         44745 VIRUS
          5102 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L15      23476 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l15 and (HR1 or HR2)
           162 HR1
```

```
           151 HR2
L16         13 L15 AND (HR1 OR HR2)

=> d his

     (FILE 'HOME' ENTERED AT 02:53:18 ON 02 OCT 2006)

     FILE 'USPATFULL' ENTERED AT 02:55:22 ON 02 OCT 2006
                E DELMEDICO MARY KAY/IN
L1            1 S E3
                E DWYER JOHN/IN
L2           31 S E3-E11
L3            2 S L2 AND (HR1 OR HR2)
L4            1 S L3 NOT L1

     FILE 'WPIDS' ENTERED AT 02:57:20 ON 02 OCT 2006
                E DELMEDICO M K/IN
L5            4 S E3
                E DWYER JOHN/IN
                E DWYER J/IN
L6           13 S E3
L7            2 S L6 AND (HR1 OR HR2)

     FILE 'MEDLINE' ENTERED AT 02:58:37 ON 02 OCT 2006
                E DELMEDICO M K/AU
L8            2 S E3 OR E4
                E DWYER JOHN/AU
L9            5 S E3
L10           5 S L9 NOT L8

     FILE 'USPATFULL' ENTERED AT 02:59:36 ON 02 OCT 2006
L11       47774 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12         136 S L11 AND (HR1 OR HR2)
L13           8 S L12 AND (HR1/CLM OR HR2/CLM)
L14           7 S L13 NOT L1

     FILE 'WPIDS' ENTERED AT 03:00:38 ON 02 OCT 2006
L15       23476 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L16          13 S L15 AND (HR1 OR HR2)

=> s l16 not l5
L17         10 L16 NOT L5

=> d l17,bib,ab,1-10

L17  ANSWER 1 OF 10  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   2006-194155 [20]    WPIDS
DNN  N2006-167236        DNC C2006-064627
TI   New primer combination comprising a set of bi-direction sequencing primers
     encompassing a region comprising the HR1 and HR2 domains of HIV-1,
     useful for detecting the presence or absence of a mutation in the nucleic
     acid of a pathogen.
DC   B04 D16 S03
IN   KEMP, S; UZGIRIS, A
PA   (FARB) BAYER HEALTHCARE LLC
CYC  111
PI   WO 2006023768   A2 20060302 (200620)* EN   67
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT
            KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ
            UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
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DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI
NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT
TZ UA UG US UZ VC VN YU ZA ZM ZW

ADT WO 2006023768 A2 WO 2005-US29618 20050819

PRAI US 2004-603337P 20040820; US 2004-603195P 20040820

AB WO2006023768 A UPAB: 20060323

NOVELTY - A primer combination comprising a set of bi-direction sequencing primers encompassing a region comprising the **HR1** and **HR2** domains of **HIV**-1, is new.

DETAILED DESCRIPTION - The primer combination comprises:

(a) a forward primer selected from the group consisting of one or more of SEQ ID Nos. 2-14, all given in the specification, or their fragments of 15 or more nucleotides; and

(b) a reverse primer selected from SEQ ID Nos. 15-30, all given in the specification, and their fragment of 15 or more nucleotides.

INDEPENDENT CLAIMS are also included for:

(1) detecting the presence or absence of a mutation of interest in the nucleic acid of a pathogen, where the mutation of interest is located adjacent to a length polymorphism defining multiple quasispecies of the pathogen, comprising: obtaining from the patient sample a double-stranded DNA template encompassing the mutation of interest; sequencing a first strand of a region of the DNA template containing the mutation of interest; sequencing a second strand of a region of the DNA template containing the mutation of interest, where the region of the DNA template sequenced that is common to the first strand and second strand excludes the length polymorphism; and comparing the sequence of the first strand with the sequence of the second strand to obtain complementary strand confirmation of the sequence of the mutation of interest; and

(2) a kit for detecting the presence or absence of a mutation of interest in a pathogen in a sample containing multiple quasispecies of the pathogen having mixed length polymorphisms, where the mutation of interest is located adjacent to the length polymorphism, comprising a first primer for sequencing a first strand of a region of a DNA template containing the mutation of interest and a second primer for sequencing a second strand of a region of the DNA template containing the mutation of interest, where the region defined by the first primer and second primer excludes the length polymorphism.

USE - The primer combination, method and kit are useful for detecting the presence or absence of a mutation of interest in the nucleic acid of a pathogen, where the mutation of interest is located adjacent to a length polymorphism defining multiple quasispecies of the pathogen (claimed).

Dwg.0/0

L17 ANSWER 2 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2006-039490 [04] WPIDS

DNC C2006-014411

TI New **HIV** antibody comprising a binding portion that interacts with the heptad repeat 1 region of the ectodomain of gp41, useful for treating **HIV** infections.

DC B04 D16

IN BIANCHI, E; ECKERT, D M; GELEZIUNAS, R; HAZUDA, D J; KIM, P S; LENNARD, S N; MILLER, M D; ROOT, M J; SHIVER, J W

PA (CAMB-N) CAMBRIDGE ANTIBODY TECHNOLOGY; (RICE-N) IST RICERCHE BIOL MOLECOLARE ANGELETTI; (MERI) MERCK CO INC; (WHED) WHITEHEAD INST BIOMEDICAL RES

CYC 111

PI WO 2005118887 A2 20051215 (200604)* EN 96

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI
NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT
TZ UA UG US UZ VC VN YU ZA ZM ZW

ADT WO 2005118887 A2 WO 2005-US19049 20050531

PRAI US 2004-576012P 20040601

AB WO2005118887 A UPAB: 20060116

NOVELTY - An isolated **HIV** antibody comprising an antibody-binding portion that interacts with a conformational epitope within a groove of adjacent coils of a trimeric pre-hairpin intermediate structure of the heptad repeat 1 region of the ectodomain of gp41, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) identifying a **HIV** antiviral compound;

(2) an **HIV** antiviral compound selected by the method, where the compound is an inorganic small molecule or peptide;

(3) treating a **HIV** positive subject;

(4) vaccinating a human subject against infection or progression of **HIV**;

(5) a pharmaceutical composition, comprising:

(a) **HIV** antibody above; and,

(b) optionally, a pharmaceutical carrier;

(6) a purified nucleic acid molecule encoding a biologically relevant portion of an antibody that interacts with a hydrophobic pocket within the heptad repeat 1 region of the ectodomain of the **HIV** transmembrane glycoprotein gp41, this DNA molecule comprising the nucleotide sequence comprising fully defined around 357-723 bp (odd SEQ ID NOs between SEQ ID NO:1-11) given in the specification;

(7) an expression vector for expressing a portion of an antibody that interacts with a hydrophobic pocket within the heptad repeat 1 region of the ectodomain of the **HIV** transmembrane glycoprotein gp41 where the expression vector comprises a nucleic acid molecule above;

(8) a cultured host cell which expresses a recombinant portion of an antibody that interacts with a hydrophobic pocket within a groove of adjacent coils of a trimeric pre-hairpin intermediate structure of the heptad repeat 1 region of the ectodomain of gp41 where the host cell contains the expression vector;

(9) expressing a portion of an antibody that interacts with a hydrophobic pocket within the heptad repeat 1 region of the ectodomain of the **HIV** transmembrane glycoprotein gp41 host cell; and

(10) an isolated antibody, specific binding member or its portion that interacts with a hydrophobic pocket within a groove of adjacent coils of a trimeric pre-hairpin intermediate structure of the heptad repeat 1 region of the ectodomain of gp41 and is substantially free from heterogeneous proteins, the antibody, specific binding member or its portion which comprises an amino acid sequence comprising fully defined around 107-241 amino acids (even SEQ ID NOs between SEQ ID NO:2-12) given in the specification.

ACTIVITY - Anti-**HIV**.

No biological data given.

MECHANISM OF ACTION - Gene therapy; Vaccine.

USE - The antibody is useful for treating **HIV** infections.

Dwg.0/17

L17 ANSWER 3 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2005-810532 [82] WPIDS

DNC C2005-249146

TI **HIV** glycoprotein 41-derived peptide for treating **HIV** infection comprises amino acid with a protected side chain amine for protecting from reactive functionality and amino acid with unprotected amine for reacting with reactive functionality.

DC A96 B05
IN BRAY, B; ZHANG, H
PA (TRIM-N) TRIMERIS INC
CYC 109
PI WO 2005089796 A1 20050929 (200582)* EN 115
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2005089796 A1 WO 2005-US7486 20050308
PRAI US 2004-553063P 20040315
AB WO2005089796 A UPAB: 20051222

NOVELTY - An isolated **HIV** glycoprotein(gp)41-derived peptide (I) having amino acid(s) containing side chain amine comprises amino acid(s) (a1) having its side chain amine chemically reacted with chemical protecting agent that protects the amine from chemical reactivity with amine-reactive functionality, and amino acid(s) (a2) having an amine unprotected and free for reacting with amine-reactive functionality; selected from an N-terminal amine and/or a side chain amine.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) method (M) for site-specific chemical modification of **HIV** glycoprotein (gp)41-derived peptide (I) having at least one amino acid with a side chain amine involving: incorporating into the peptide or its fragment at least one (a1) and at least one (a2), during the peptide synthesis; and

(2) method (M1) for producing a substantially homogeneous conjugate of **HIV** gp41-derived peptide and polymer involving: synthesizing (I) having at least one amino acid with a side chain amine by method (M); and covalently coupling a polymer to (I) by chemically reacting the amine-reactive functionality of the polymer to a free amine group of (I), such that the polymer is covalently coupled only to amino acid(s) having a free amine, and not to amino acid(s) protected by the chemical protecting agent.

ACTIVITY - Anti-**HIV**.

An **HIV** gp41-derived peptide-conjugate comprising T20 (a peptide derived from **HR2** (heptad region 2) of **HIV**) peptide having a sequence Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe, having protected side chain amines of Lys at positions 18 and 28, and having conjugated 2K polyethylene glycol (PEG) site-specifically conjugated to the N-terminal amine, was tested for anti-**HIV** activity, by an in vitro Magi-CCR5 (chemokine receptor 5) infectivity assay, as described in US6258782. T20 showed IC50 of less than 0.02 mu g/ml.

MECHANISM OF ACTION - **HIV** transmission inhibitor; **HIV** fusion inhibitor.

USE - For producing a substantially homogeneous conjugate of **HIV** gp41-derived peptide and polymer; useful for the manufacture of a medicament for treatment of **HIV** infection (claimed).

ADVANTAGE - The **HIV** gp41-derived peptides contain site-specific modifications for allowing covalent coupling to the activated polyethylene glycol (PEG) polymer, during the formation of PEGylated peptide, at the desired sites and in desired amount. The peptides contain amino acid(s) having side chain amine chemically protected and amino acid(s) having an unprotected free amine, for protection from coupling and coupling with reactive PEG molecules, respectively; thus provide site-specific PEGylation by reaction only with the unprotected amines, and results in substantially homogeneous conjugates. The method avoids the cross-linking

of the branched PEG molecule by allowing attachment of selected amines and avoiding attachment to multiple amines. Thus avoids the heterogeneity due to variation in the number and sites of PEG molecules attached, and maintains the pharmacological and/or biological properties of the PEGylated conjugates of **HIV** gp41-derived peptides.
Dwg.0/6

L17 ANSWER 4 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2005-591973 [60] WPIDS
DNC C2005-178417
TI Novel fusion protein exhibiting anti-viral activity, comprising helix forming region 2 of ectodomain of **HIV** gp41 protein, and multimerization domain peptide, useful for treating **HIV** infection.
DC B04 D16
IN ETZERODT, M
PA (BORE-N) BOREAN PHARMA AS
CYC 108
PI WO 2005080418 A2 20050901 (200560)* EN 103
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2005202043 A1 20050915 (200561)
ADT WO 2005080418 A2 WO 2005-DK121 20050223; US 2005202043 A1 Provisional US 2004-546200P 20040223, US 2005-64115 20050223
PRAI US 2004-546200P 20040223; DK 2004-283 20040223
AB WO2005080418 A UPAB: 20050920
NOVELTY - A fusion protein (I) exhibiting anti-viral activity, comprising a first polypeptide representing the helix forming region 2 (**HR2**) of the ectodomain of **HIV** gp41 protein or its portion, and a second polypeptide representing a multimerization domain peptide, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a polypeptide complex (II) comprising at least 2-6 of (I), preferably three of (I);
(2) a pharmaceutical composition comprising (I) or (II);
(3) producing (II), involves expressing or synthesizing (I), effecting complex formation between proteins of (I), and isolating the resulting (II) and optionally subjecting (II) to further processing;
(4) a composition comprising (I) or (II);
(5) an isolated nucleic acid sequence (NS) encoding (I);
(6) a recombinant vector (V1) comprising NS; and
(7) a host cell transformed with V1.
ACTIVITY - Anti-**HIV**. In vitro analysis of the antiviral activity of BPFI-0300 was carried out as follows. **HIV**-1 strain IIIB was propagated in H9 cells at 37 deg. C, in RPMI 1640 medium supplemented with heat inactivated fetal calf serum (FCS) (10 %) and standard antibiotics, in the presence of carbon dioxide (5 %). The culture supernatants were filtered. MT4 cells were incubated with the virus (0.005 MOI) and growth medium containing dilutions of the test compound (BPFI-0300) for 6 days in parallel with virus-infected and uninfected control cultures without added compound. Compound and buffers were also tested in parallel for cytotoxic effects in uninfected MT4 cultures. The BPFI fusion protein was found to exhibit antiviral activity.
MECHANISM OF ACTION - **HIV** fusion inhibitor.
USE - (I) or (II) is useful for treating **HIV** infection in a subject, which involves administering (II) to the subject. The method further involves administering at least one further therapeutic agent. (I)

or (II) is useful for the preparation of a pharmaceutical composition (claimed). (I) is useful as **HIV** fusion inhibitor.

ADVANTAGE - (I) being an **HIV** fusion inhibitor has higher efficacy in preventing the evolution of escape mutants, and has increased plasma half-life and increased product uniformity and purity.

Dwg.0/6

L17 ANSWER 5 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2005-056024 [06] WPIDS
CR 2006-537770 [55]
DNC C2005-019210
TI Pharmaceutical composition useful for treating viral infections such as AIDS, has amino-modified polysaccharide having amino group linked to peptide composed of some basic amino acid residues.
DC A11 A96 B04 D16
IN BORKOW, G; LAPIDOT, A; VIJAYABASKAR, V
PA (BORK-I) BORKOW G; (LAPI-I) LAPIDOT A; (VIJA-I) VIJAYABASKAR V
CYC 1
PI US 2004229265 A1 20041118 (200506)* 45
ADT US 2004229265 A1 Provisional US 2003-465775P 20030428, US 2004-831224 20040426
PRAI US 2003-465775P 20030428; US 2004-831224 20040426
AB US2004229265 A UPAB: 20060825

NOVELTY - A pharmaceutical composition (I), comprising as an active ingredient, an amino-modified polysaccharide having at least one amino group linked to a peptide composed of at least two basic amino acid residues, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a pentaargininamido-paromomycin conjugate (ParomR5);

(2) an argininamido-paramomycin conjugate (ParomR1) of formula (I);

(3) a tetraargininamido-neamine conjugate;

(4) an argininamido-neamine conjugate (NeamR1) of formula (II);

(5) a diargininamido-neomycin B conjugate (NeoR2) of formula (III);

(6) an argininamido-neomycin B conjugate (NeoR1) having formula (IV) or (V);

(7) selectively protecting (M1) an alkyl amino group of a polyamino cyclic compound, comprising attaching an N-protecting group to the alkyl amino group of the polyamino cyclic compound, the N-protecting group having a size selected suitable for selectively reacting with the alkyl amino group, to thus selectively protect the alkyl amino group of the polyamino cyclic compound;

(8) generating (M2) a saccharide-chemical moiety site specific conjugate, by:

(a) providing a saccharide having a reactive alkyl amino group and protected non-alkyl amino reactive groups; and

(b) reacting the saccharide with a chemical moiety;

(9) identifying (M3) a potent anti **HIV** agent, by:

(a) providing several putative anti **HIV** agents; and

(b) identifying an anti **HIV** agent of the several putative anti **HIV** agents incapable of inducing mutational instability in a predetermined sequence region of gp120, gp41 and/or CXCR4; and

(10) generating (M4) an oligo-saccharide, by:

(a) providing at least two saccharides each having at least one reactive alkyl amino group and protected non-alkyl amino reactive group; and

(b) reacting at least two saccharides.

ACTIVITY - Anti-**HIV**; Antiinflammatory; Hepatotropic; Virucide; Antibacterial; Antitubercular; Tuberculostatic.

MECHANISM OF ACTION - Binds to viral target such as Rev responsive element (RRE); Inhibitor of viral proliferation.

The ability of viral inhibition by aminoglycoside-arginine conjugates (AACs) was determined by incubating cMAG1 **HIV**-1 reporter cells with 0.2-0.5 multiplicity of infections of **HIV**-1(IIIB) for 4 days at 37 deg. C in the presence or absence of various concentration of AACs, prior to counting the number of **HIV**-1 infected cells. The presence of R3G or NeoR6 inhibited viral proliferation through viral infection, but more importantly through the first two hours of viral infection, indicating that the AACs inhibited the first stages of **HIV**-1 infectivity, and/or that the AACs were taken readily into the cells, and inhibited subsequent viral infectivity steps.

USE - (I) is useful for treating a viral infection in a subject (claimed). (I) is useful for treating viral infections such as AIDS, infections caused by equine infectious anemia virus and hepatitis C viral infections, and bacterial infections such as infections caused by aerobic gram-negative bacteria such as Bacilli such as Pseudomonas, and gram-positive bacteria such as Mycobacteria which causes tuberculosis-like diseases.

ADVANTAGE - The amino modified polysaccharides of (I) displays improved therapeutic efficacy.

DESCRIPTION OF DRAWING(S) - The figure shows inhibitory effects of NeoR6 and R3G on replication of **HIV**-1 clade C in MT2 cells.

7a, 7b/14

L17 ANSWER 6 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2004-806342 [80] WPIDS

DNC C2004-281501

TI Rendering a virus dependent on an inducing agent for viral entry comprises increasing the affinity between a **HR1** domain and a **HR2** domain of the envelope glycoprotein of the virus to such extent that the pairing occurs.

DC B04 D16

IN BALDWIN, C E; BERKHOUT, B

PA (MEDI-N) ACAD MEDISCH CENT AMSTERDAM

CYC 109

PI EP 1479774 A1 20041124 (200480)* EN 31
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
WO 2004104033 A2 20041202 (200480) EN
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

ADT EP 1479774 A1 EP 2003-76521 20030520; WO 2004104033 A2 WO 2004-NL349 20040519

PRAI EP 2003-76521 20030520

AB EP 1479774 A UPAB: 20041213

NOVELTY - Rendering a virus dependent on an inducing agent for viral entry by means of a pairing of two domains (**HR1** and **HR2**) of an envelope glycoprotein into a host cell, where the inducing agent is capable of interfering in the pairing.

DETAILED DESCRIPTION - Rendering a virus dependent on an inducing agent for viral entry by means of a pairing of two domains (**HR1** and **HR2**) of an envelope glycoprotein into a host cell, where the inducing agent is capable of interfering in the pairing, comprises increasing the affinity between a **HR1** domain and a **HR2** domain of the envelope glycoprotein of the virus to such extent that the pairing occurs without the presence of a host cell (a premature switch) when the inducing agent is essentially not present.

INDEPENDENT CLAIMS are included for the following:

(1) a virus dependent on an inducing agent for viral entry obtainable by the novel method;

(2) a viral replicon comprising a nucleic acid sequence with a mutation in a region encoding a **HR1** domain and/or **HR2** domain of an envelope glycoprotein, resulting in an increased affinity between the **HR1** domain and the **HR2** domain to such extent that pairing of the **HR1** and **HR2** domains occurs without the presence of a host cell when an inducing agent is essentially not present;

(3) a method for producing a virus dependent on an inducing agent for viral entry, comprising providing a permissive cell with the virus and/or a viral replicon; culturing the cell; and harvesting the dependent virus from the culture;

(4) a vaccine comprising the virus and/or viral replicon;

(5) a kit of parts comprising the virus and/or viral replicon, and an amount of inducing agent;

(6) a method for the controlled replication of the virus and/or viral replicon comprising providing a permissive cell with the virus and/or replicon; culturing the cell in the presence of the inducing agent and manipulating the amount of inducing agent present;

(7) a method for the prophylaxis of AIDS by administering the vaccine or kit to a patient; and allowing for viral entry for a limited time by providing the inducing agent;

(8) a method for modifying the virus and/or viral replicon by generating the virus and/or viral replicon; providing cells, permissive for replication of the virus and/or replicon with the virus and/or replicon; culturing the cells under conditions that allow replication of the virus and/or replicon; obtaining replicated virus and/or replicon from the culture;

(9) a viral nucleic acid sequence comprising a mutation in a region encoding a **HR1** domain and/or **HR2** domain of an envelope glycoprotein resulting in an increased affinity between the **HR1** domain and the **HR2** domain to such extent that pairing of the **HR1** and **HR2** domains occurs when an inducing agent is essentially not present;

(10) an isolated or recombinant proteinaceous molecule capable of specifically binding the virus; and

(11) a cell comprising the replicon, or the nucleic acid.

USE - The method is useful for rendering a virus dependent on an inducing agent for viral entry by means of a pairing of two domains (**HR1** and **HR2**) of an envelope glycoprotein into a host cell (claimed).

Dwg.0/9

L17 ANSWER 7 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2004-635152 [61] WPIDS
DNC C2004-228269
TI New betulinic acid derivatives useful for inhibiting growth of tumors, e.g. melanomas and neuroectodermal tumors, or for treating sarcomas and **human immunodeficiency virus** infections.
DC B01
IN JANSEN, B; PASCHKE, R; SELZER, E
PA (NOVE-N) NOVELIX PHARM INC; (SELZ-I) SELZER E
CYC 109
PI WO 2004072092 A1 20040826 (200461)* GE 22
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2004210714 A1 20040826 (200557)
EP 1594885 A1 20051116 (200575) GE

R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
JP 2006517208 W 20060720 (200648) 18
CN 1747964 A 20060315 (200649)
US 2006194774 A1 20060831 (200657)
ADT WO 2004072092 A1 WO 2004-AT45 20040211; AU 2004210714 A1 AU 2004-210714 20040211; EP 1594885 A1 EP 2004-709952 20040211, WO 2004-AT45 20040211; JP 2006517208 W WO 2004-AT45 20040211, JP 2006-501337 20040211; CN 1747964 A CN 2004-Y3907 20040211; US 2006194774 A1 WO 2004-AT45 20040211, US 2005-545143 20050810
FDT AU 2004210714 A1 Based on WO 2004072092; EP 1594885 A1 Based on WO 2004072092; JP 2006517208 W Based on WO 2004072092
PRAI AT 2003-200 20030211
AB WO2004072092 A UPAB: 20040923
NOVELTY - Betulinic acid derivatives (I) are new.
DETAILED DESCRIPTION - Betulinic acid derivatives of formula (I) and their salts and clathrates are new.
R1 = optionally protected OH or amino;
R2 = OCH2C(CH2OH)3, OCH2C(CH2OH)2CH2NH2, OCH2C(CH2OCH2COOH)3, NHCH2C(CH2OCH2COOH)2CH2OH, OCH2C(CH2OCH2COOH)2CH2NH2 or NHCH2C(CH2OH)3.
An INDEPENDENT CLAIM is also included for a process for preparing (I).
ACTIVITY - Cytostatic; Anti-**HIV**; Antiinflammatory.
Acetylbetulinic acid 2-amino-3-hydroxy-2-(hydroxymethyl)propyl ester had an EC50 of 0.7 mu g/ml against growth of 518A2 melanoma cells, compared with 5 mu g/ml for betulinic acid.
MECHANISM OF ACTION - None given.
USE - (I) are useful as pharmaceuticals, for preparing medicaments for inhibiting growth of tumors, e.g. melanomas and neuroectodermal tumors, or for treating sarcomas and **HIV**, and for preparing medicaments for combination therapy with other cytostatic substances and cell death modulators, e.g. antisense oligonucleotides against anti-apoptotic Bcl-2 family members, especially Bcl-2, Bcl-xL and Mcl-1 (all claimed). (I) are also useful for treating nonspecific inflammatory diseases.
Dwg.0/0

L17 ANSWER 8 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2004-375438 [35] WPIDS
DNC C2004-141075
TI Conjugate useful for treating **HIV**-infected individual, comprises polymer operably bound to not less than two synthetic peptides derived from heptad repeat region of **HIV** gp41 by reactive functionality.
DC A96 B04 D16
IN BRAY, B; KANG, M; KINDER, D; LACKEY, J W; TVERMOES, N; ZHANG, H; ZHANG, Y; KANG, M C
PA (BRAY-I) BRAY B; (KANG-I) KANG M; (KIND-I) KINDER D; (LACK-I) LACKEY J W; (TVER-I) TVERMOES N; (TRIM-N) TRIMERIS INC
CYC 103
PI WO 2004029073 A2 20040408 (200435)* EN 79
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
US 2004122214 A1 20040624 (200442)
AU 2003278937 A1 20040419 (200462)
EP 1554306 A2 20050720 (200547) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR

BR 2003014707 A 20050726 (200551)
CN 1684972 A 20051019 (200612)
KR 2005046780 A 20050518 (200641)

ADT WO 2004029073 A2 WO 2003-US30285 20030926; US 2004122214 A1 Provisional US 2002-414439P 20020927, US 2003-671282 20030924; AU 2003278937 A1 AU 2003-278937 20030926; EP 1554306 A2 EP 2003-770450 20030926, WO 2003-US30285 20030926; BR 2003014707 A BR 2003-14707 20030926, WO 2003-US30285 20030926; CN 1684972 A CN 2003-823021 20030926; KR 2005046780 A WO 2003-US30285 20030926, KR 2005-704391 20050315

FDT AU 2003278937 A1 Based on WO 2004029073; EP 1554306 A2 Based on WO 2004029073; BR 2003014707 A Based on WO 2004029073; KR 2005046780 A Based on WO 2004029073

PRAI US 2003-671282 20030924; US 2002-414439P 20020927

AB WO2004029073 A UPAB: 20040603

NOVELTY - A conjugate (I) comprising a polymer operably bound to not less than 2 synthetic peptides, where each peptide is operably bound to polymer by a reactive functionality, comprises sequence derived from a heptad repeat region of **HIV** gp41, and comprises sequence of not less than 16 amino acids and not more than 60 amino acids, and where (I) has durability comprising antiviral activity against **HIV** strains resistant to synthetic peptide alone.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for making (M1) (I), involves reacting a first molecule of synthetic peptide with a polymer in forming an intermediate comprising a first intermediate, where the first molecule of synthetic peptide operably binds to a first reactive functionality of the polymer, and reacting the intermediate comprising the first intermediate with a second molecule of synthetic peptide, where the second molecule of synthetic peptide operably binds to the intermediate comprising the first intermediate by a second reactive functionality of the polymer, in forming (I).

ACTIVITY - Anti-**HIV**. No supporting data is given.

MECHANISM OF ACTION - Inhibitor of gp41-mediated fusion of **HIV**-1 to a target cell.

USE - (I) is useful for inhibiting transmission of **HIV** to a target cell, which involves adding (I) to the virus and the cell. (I) inhibits fusion between the virus and the target cell in inhibiting infection of the cell by the virus. (I) further comprises a carrier. (I) is administered to an **HIV**-infected individual (claimed).

ADVANTAGE - (I) has the advantage of retaining substantial biological activity such as antiviral activity against **HIV**, and exhibiting durability as compared to synthetic peptide alone without being a part of (I). (I) increases the biological half-life of the synthetic peptide.

DESCRIPTION OF DRAWING(S) - The figure shows a schematic of **HIV**-1 gp41 showing the heptad repeat 1 (**HR1**) and **HR2** along with other functional regions of gp41.

Dwg.1/3

L17 ANSWER 9 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2002-061972 [08] WPIDS

DNC C2002-017633

TI New human polypeptides associated with reproduction, for treating and preventing reproductive, cell proliferative, endocrine, immune, infectious, metabolic and developmental disorders.

DC B04 D16

IN AZIMZAI, Y; HILLMAN, J L; TANG, Y T

PA (INCY-N) INCYTE GENOMICS INC; (AZIM-I) AZIMZAI Y; (HILL-I) HILLMAN J L; (TANG-I) TANG Y T

CYC 95

PI WO 2001079282 A2 20011025 (200208)* EN 97

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001053388 A 20011030 (200219)
EP 1272511 A2 20030108 (200311) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
US 2004053240 A1 20040318 (200421)
JP 2004518401 W 20040624 (200442) 184
AU 2001253388 A8 20050908 (200568)

ADT WO 2001079282 A2 WO 2001-US11858 20010411; AU 2001053388 A AU 2001-53388 20010411; EP 1272511 A2 EP 2001-926880 20010411, WO 2001-US11858 20010411; US 2004053240 A1 WO 2001-US11858 20010411, US 2002-257898 20021015; JP 2004518401 W JP 2001-576877 20010411, WO 2001-US11858 20010411; AU 2001253388 A8 AU 2001-253388 20010411

FDT AU 2001053388 A Based on WO 2001079282; EP 1272511 A2 Based on WO 2001079282; JP 2004518401 W Based on WO 2001079282; AU 2001253388 A8 Based on WO 2001079282

PRAI US 2000-197767P 20000414; US 2002-257898 20021015

AB WO 200179282 A UPAB: 20020204

NOVELTY - An isolated human polypeptide (I) associated with reproduction and designated as HR polypeptide (**HR1** or **HR2**), comprising a sequence (S1) of 706 or 453 amino acids, given in the specification, a naturally occurring polypeptide sequence having at least 90 % identity to S1, or a biologically active or immunogenic fragment of S1, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polynucleotide (II) encoding (I);

(2) a recombinant polynucleotide (III) comprising a promoter sequence operably linked to (II);

(3) a cell transformed with (III);

(4) a transgenic organism comprising (III);

(5) producing (I) comprising culturing (3) and recovering (I);

(6) an isolated antibody (Ab) which specifically binds to (I);

(7) an isolated polynucleotide (IIa) comprising a sequence (S2) of 2653 or 1730 nucleotides, given in the specification, a naturally occurring polynucleotide sequence having at least 90 % identity to S2, a polynucleotide sequence complementary to the polynucleotides, or an RNA equivalent of the polynucleotides;

(8) an isolated polynucleotide (IIb) comprising at least 60 contiguous nucleotides of (IIa);

(9) detecting (IIa) in a sample, by:

(a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to (IIa) in the sample, where the probe specifically hybridizes to (IIa) under conditions such that a hybridization complex is formed between the probe and (IIa) or its fragments, and detecting the presence or absence of the hybridization complex, and optionally, if present, the amount of the complex; or

(b) amplifying the target polynucleotide or its fragment using polymerase chain reaction (PCR) amplification and detecting the presence or absence of the amplified target polynucleotide or its fragment, and optionally, if present, the amount of the amplified product;

(10) a composition (C1) comprising (I), an agonist or antagonist compound identified by using (I);

(11) preparing a polyclonal antibody with the specificity of Ab, by immunizing an animal with (I), or its immunogenic fragment, under conditions to elicit an antibody response, isolating antibodies from the animal, and screening the isolated antibodies with (I), and thus identifying a polyclonal antibody which binds specifically to (I);

(12) an antibody (Ab1) produced by (11);

(13) making a monoclonal antibody with the specificity of Ab, by:

(a) immunizing an animal with (I), or its immunogenic fragment, under conditions to elicit an antibody response;

(b) isolating antibody producing cells from the animal;

(c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells;

(d) culturing the hybridoma cells; and

(e) isolating from the culture the monoclonal antibody which binds specifically to (I);

(14) a monoclonal antibody (MAb) produced by (13); and

(15) a composition (C2) comprising Ab, Ab1 or MAb.

ACTIVITY - Antiarteriosclerotic; hepatotropic; anti-HIV; antiinflammatory; antipsoriatic; cytostatic; antiinfertility; antithyroid; antiallergic; antianemic; antiasthmatic; virucide; dermatological; antidiabetic; osteopathic; immunosuppressive; antiulcer; antirheumatic; antiarthritic; antibacterial; fungicide; antiparasitic; nephrotropic; ophthalmological.

MECHANISM OF ACTION - Gene therapy; vaccine. No biological data is given.

USE - (I) is used for screening a compound:

(a) for effectiveness as an agonist or antagonist, by exposing a sample comprising (I) to a compound and detecting agonist or antagonist activity in the sample;

(b) that specifically binds (I), by combining (I) with a test compound and detecting binding of (I) to the test compound; and

(c) that modulates the activity of (I), by combining (I) with a test compound and comparing the activity of (I) in the presence or absence of the test compound.

A nucleic acid (II) encoding (I) is used for screening a compound for effectiveness in altering expression of a target polynucleotide comprising S2, by exposing a sample comprising the target polynucleotide to a compound, detecting altered expression of the target polynucleotide, and comparing the expression of the target polynucleotide in the absence or presence of varying amounts of the compound. Nucleic acid (IIb) is used for assessing toxicity of a test compound, by treating a biological sample containing nucleic acids with the test compound, hybridizing the nucleic acids of the treated biological sample with (IIb), quantifying the amount of hybridization complex formed, and comparing the amount of the complex in treated or untreated biological samples. An antibody (Ab) to (I) is used in a diagnostic test for a condition or a disease associated with the expression of HR in a biological sample, by combining the biological sample with Ab, and detecting an antibody:polypeptide complex formed. Ab is useful for detecting (I) in a sample, by incubating Ab with a sample and detecting specific binding. Ab is also used for purifying (I) from a sample, by incubating Ab with a sample, separating the antibody from the sample and obtaining the purified (I). A composition comprising an antagonist is useful for treating a disease or condition associated with decreased or increased expression of functional HR. A composition comprising an antibody is useful for diagnosing a condition or disease associated with the expression of HR in a subject (all claimed). (I) and (II) are useful for diagnosing, treating and preventing cell proliferative (e.g. arteriosclerosis, atherosclerosis, hepatitis, psoriasis and cancers), reproductive (e.g. infertility, endometriosis, ovarian tumor, and ectopic pregnancy), endocrine (e.g. disorders associated with hypopituitarism (diabetes insipidus), hyperpituitarism (acromegaly), hypothyroidism (goiter), hyperthyroidism (Grave's disease), hyperparathyroidism (Conn disease), pancreatic (diabetes mellitus), adrenal (Addison's disease), and gonadal (amenorrhea)), immune (e.g. inflammation, anemia, asthma, atopic dermatitis, acquired immunodeficiency syndrome (AIDS), hepatitis, rheumatoid arthritis, irritable bowel syndrome, osteoporosis, psoriasis, and ulcerative colitis), infectious including viral, bacterial, fungal and parasitic, metabolic (e.g. cystic fibrosis), and developmental disorders (e.g. renal tubular acidosis,

Cushing's syndrome, Duchenne and Becker muscular dystrophy, seizure disorders, congenital glaucoma and cataract). (II) is used for creating knockin humanized animals or transgenic animals to model human diseases. (II) is also used in somatic or germline gene therapy. (II) is used for detecting differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier or affected individuals. (II) is used as hybridization probes for mapping naturally occurring genomic sequences. (I) is used in a number of drug screening techniques.
Dwg.0/0

L17 ANSWER 10 OF 10 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2000-514889 [46] WPIDS
DNC C2000-153639
TI Administering T-20 to a host to depress retrovirus titre in vivo for treating retroviral disease, especially AIDS.
DC B04
IN KAPPES, J C; SHAW, G M; WU, X
PA (UABR-N) UAB RES FOUND
CYC 82
PI WO 2000045833 A1 20000810 (200046)* EN 22
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 2000032205 A 20000825 (200059)
ADT WO 2000045833 A1 WO 2000-US2643 20000202; AU 2000032205 A AU 2000-32205 20000202
FDT AU 2000032205 A Based on WO 2000045833
PRAI US 1999-118283P 19990202
AB WO 200045833 A UPAB: 20000921
NOVELTY - Depressing retrovirus titre in vivo involves administering T-20 (a sythetic peptide) to the host with a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a compound with an amino acid sequence (S1) comprising at least 10 amino acids (aa) of consensus 1 as given in the specification (113 aa), a mutant of (S1), **HR2** of **HIV**-1 gp41, **HR2** of **HIV**-2 gp41, **HR2** of SIV or its functional equivalent which reduces retrovirus titre in an infected host upon administration.

ACTIVITY - Antiviral; anti-**HIV**.

T-20 was administered to 12 patients (in doses of 3, 10, 30 and 100 mg bid) of and drug resistance was determined. After 2 weeks of intravenous T-20 therapy, genetic and biological evidence of resistance was observed in 1 of 12 subjects studied. Evidence of drug resistance was found in a single subject who was treated with suboptimal doses (30 mg bid) of T-20 and not in any of the 4 subjects treated with highest dosage (100 mg bid) levels.

MECHANISM OF ACTION - Blocks **HIV**-1 entry.

USE - For treating viral infections, preferably **HIV** infections and diseases.

ADVANTAGE - T-20 has an IC50 value of 0.5-50 micro g/ml.
Dwg.0/11

=> file medline
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	43.34	103.28

```
FILE 'MEDLINE' ENTERED AT 03:01:16 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP). FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available. For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (HIV or human immunodeficiency virus)
        163348 HIV
       1420903 HUMAN
        124822 IMMUNODEFICIENCY
        419508 VIRUS
         49412 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L18     168740 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l18 and (HR1 or HR2)
           250 HR1
           202 HR2
L19         59 L18 AND (HR1 OR HR2)

=> d l19,cbib,ab,1-59

L19  ANSWER 1 OF 59     MEDLINE on STN
2006511872.    PubMed ID: 16927284.   A cohort study of enfuvirtide
     immunological and virological efficacy in clinical practice. Bienvenu
     Boris; Krivine Anne; Rollot Florence; Pietri Marie-Pierre; Lebault
     Valerie; Meritet Jean-Francois; Guerin Corinne; Spiridon Gabriela; Salmon
     Dominique; Guillevin Loic; Lebon Pierre; Launay Odile. (Universite Paris
     Descartes, Faculte de medecine, Paris, France. ) Journal of medical
     virology, (2006 Oct) Vol. 78, No. 10, pp. 1312-7. Journal code: 7705876.
     ISSN: 0146-6615. Pub. country: United States. Language: English.
AB   The aim of the study was to evaluate, under routine circumstances, the
     immunological and virological efficacy of antiretroviral regimens
     containing enfuvirtide in multi-class experienced HIV-1 infected
     patients. This retrospective monocentric study analyzed the clinical,
     immunological, and virological data of 18 HIV-1 infected patients who
     started enfuvirtide and completed at least 3 months of therapy. Following
     3 months of enfuvirtide therapy, 11 (61%) patients had HIV-1 RNA below
     400 copies/ml, among whom 8 (44%) patients below 50 copies/ml. In the ten
     patients still receiving enfuvirtide after 12 months, the median increase
     in CD4 cell count was 159 cells/microl (range, -25 to +301) and the mean
     decrease in HIV-1 RNA was 2.5 +/- 1.4 log(10) copies/ml; in six of these
     patients, viral load remained below 50 copies/ml. Five patients
     discontinued enfuvirtide for virological failure but none as a consequence
     of adverse event. Mutations located within the 36-45 amino acid domain of
```

HR1 region of gp41 and associated to enfuvirtide resistance were found in all seven patients with persistent viral replication. In addition, a new mutation, A50V, emerged in one patient with late viral rebound. Its disappearance after treatment discontinuation suggests that it could play a role in resistance to enfuvirtide. In conclusion, enfuvirtide may be a good therapeutic option as rescue therapy in treatment-experienced patients. However, the mutations conferring resistance to enfuvirtide develop rapidly when viral load is not controlled confirming that enfuvirtide should be prescribed in association with an active background regimen.

L19 ANSWER 2 OF 59 MEDLINE on STN

2006488305. PubMed ID: 16912327. Role of the envelope genetic context in the development of enfuvirtide resistance in **human immunodeficiency virus** type 1-infected patients. Labrosse Beatrice; Morand-Joubert Laurence; Goubard Armelle; Rochas Severine; Labernardiere Jean-Louis; Pacanowski Jerome; Meynard Jean-Luc; Hance Allan J; Clavel Francois; Mammano Fabrizio. (Inserm U552, Unite de Recherche Antivirale, Hopital Bichat-Claude Bernard, Paris, France.. labrosse@bichat.inserm.fr) . Journal of virology, (2006 Sep) Vol. 80, No. 17, pp. 8807-19. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Acquired **human immunodeficiency virus** type 1(**HIV**-1) resistance to the fusion inhibitor enfuvirtide (ENF) is primarily associated with mutations within the highly conserved first heptad repeat (**HR1**) region of gp41. Viral env sequences, however, are remarkably variable, and the envelope genetic background could have an important impact on optimal expression of **HR1** mutations. We have examined the genetic evolution of env sequences, ENF susceptibility, and Env replicative capacity in patients failing ENF treatment. Sequential plasma-derived virus populations, obtained from six patients initiating ENF treatment as part of a salvage therapy, were studied using a recombinant phenotypic assay evaluating the entire gp120 and the gp41 ectodomains. Regardless of major differences in the baseline ENF susceptibilities, viral populations with similar phenotypic ENF resistance (50% inhibitory concentration, >3,000 ng/ml) were selected under treatment in four of six patients. As expected, in all patients ENF-resistant viruses harbored one or more **HR1** mutations (positions 36, 38, and 43). Interestingly, in five patients the emergence of resistance mutations was not associated with reduced Env replicative capacity. Phylogenetic analysis of env sequences in sequential samples from two patients showed that the **HR1** mutations had emerged in the context of env quasi-species that were different from those prevalent at baseline. Thus, the envelope genetic context appears to play a critical role in the selection of **HR1** mutations and the expression of ENF resistance, thereby conditioning the evolution of **HIV**-1 under fusion inhibitor selective pressure.

L19 ANSWER 3 OF 59 MEDLINE on STN

2006437397. PubMed ID: 16765082. Genotypic changes in **human immunodeficiency virus** type 1 envelope glycoproteins on treatment with the fusion inhibitor enfuvirtide and their influence on changes in drug susceptibility in vitro. Su C; Melby T; DeMasi R; Ravindran P; Heilek-Snyder G. (Roche Pharmaceuticals, Palo Alto, CA 94304, USA.) Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, (2006 Aug) Vol. 36, No. 4, pp. 249-57. Electronic Publication: 2006-06-09. Journal code: 9815671. ISSN: 1386-6532. Pub. country: Netherlands. Language: English.

AB BACKGROUND: Previous studies have established the importance of substitutions at amino acids 36-45 of **HIV**-1 gp41 in the development of viral resistance to the peptide fusion inhibitor enfuvirtide. However, the influence of other loci in the **HIV**-1 envelope is not well established. OBJECTIVE: To identify positions showing genotypic changes

that are associated with particularly high levels of changes in enfuvirtide susceptibility. STUDY DESIGN: We examined full-length baseline and on treatment sequences of gp120 and gp41 for isolates from 369 patients in Phase III studies of enfuvirtide, including 281 patients receiving ENF+OB and 88 patients receiving OB alone. Individual changes in gp41 and gp120 were evaluated for correlations with on treatment phenotype changes by analysis of variance (ANOVA). This modeling was done with (two-way) and without (one-way) ANOVA adjusting for the effects of any changes in gp41 amino acids 36-45 modeled as a single variable (ANY(36-45)). Positions displaying significance levels of $p<0.05$ by either one- or two-way ANOVA were then studied by multi-way ANOVA (stepwise regression). RESULTS: In addition to changes at gp41 amino acids 36-45, changes at three positions in the **HR2** domain (126, 129 and 133) occurred significantly more often in patients undergoing virologic failure on enfuvirtide. However, ANY(36-45) alone accounted for slightly more than 90% of the variation in phenotype explained by the ANOVA models. Relative to ANY(36-45) alone, significant increases in the geometric mean of the fold-change in inhibitory concentration (19.6-236.3-fold higher) were observed for amino acid changes at positions gp41: 18, 42,126, 247, 256 and 312; gp120: 330, 389 and 424 and significant reductions (18.8-29.7-fold lower) for gp41: 3, 46, 165, 232 and 324. CONCLUSIONS: This study represents a statistical approach to highlight positions in **HIV** envelope that undergo mutations in the presence of enfuvirtide. Several of the identified positions have been implicated in the viral fusion process by other studies. The specific impact of positions 330. Three hundred and eighty-nine and 424 on viral fusion kinetics remains to be studied further by site-directed mutagenesis experiments.

L19 ANSWER 4 OF 59 MEDLINE on STN

2006280992. PubMed ID: 16709850. **HIV**-1 adapts to a retrocyclin with cationic amino acid substitutions that reduce fusion efficiency of gp41. Cole Amy L; Yang Otto O; Warren Andrew D; Waring Alan J; Lehrer Robert I; Cole Alexander M. (Department of Molecular Biology and Microbiology, Burnett College of Biomedical Sciences, University of Central Florida, FL 32816, USA.. acole@mail.ucf.edu) . Journal of immunology (Baltimore, Md. : 1950), (2006 Jun 1) Vol. 176, No. 11, pp. 6900-5. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Retrocyclin (RC)-101 is a cationic theta-defensin that inhibits **HIV**-1 entry. Passaging **HIV**-1(BAL) under selective pressure by this cyclic minidefensin resulted in only a 5- to 10-fold decrease in viral susceptibility to RC-101. Emergent viral isolates had three amino acid substitutions in their envelope glycoprotein. One was in a CD4-binding region of gp120, and the others were in the heptad repeat (HR) domains of gp41 (**HR1** and **HR2**). Each mutation replaced an electroneutral or electronegative residue with one that was positively charged. These mutations were evaluated either alone or in combination in a single-round viral entry assay. Although the mutation in gp120 did not affect viral entry, the mutation in **HR1** of gp41 conferred relative resistance to RC-101. Interestingly, the envelope with the **HR2** mutation was less efficient and became codependent on the presence of RC-101 for entry. The adaptive response of **HIV**-1 to this cationic host defense peptide resembles the responses of bacteria that modulate their surface or membrane charge to evade analogous host defense peptides. These findings also suggest that interactions between theta-defensins and gp41 may contribute to the ability of these cyclic minidefensins to prevent **HIV**-1 entry into target cells.

L19 ANSWER 5 OF 59 MEDLINE on STN

2006216877. PubMed ID: 16623640. Susceptibility to antiretroviral drugs of CRF01_AE, CRF02_AG, and subtype C viruses from untreated patients of Africa and Asia: comparative genotypic and phenotypic data. Fleury Herve J; Toni Thomas; Lan N T H; Hung P V; Deshpande Alaka; Recordon-Pinson

Patricia; Boucher Sebastien; Lazaro Estibaliz; Jauvin Valerie; Lavignolle-Aurillac Valerie; Lebel-Binay Sophie; Cheret Arnaud; Masquelier Bernard. (Laboratoire de Virologie UPRES EA 2968, Universite de Bordeaux 2, 33076 Bordeaux France.. herve.fleury@chu-bordeaux.fr) . AIDS research and human retroviruses, (2006 Apr) Vol. 22, No. 4, pp. 357-66. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Non-B **HIV**-1 viruses are predominant in developing countries where access to antiretroviral drugs (ARVs) is progressively being intensified. It is important to obtain more data on the susceptibility of these viruses to available ARVs. CRF01_AE, CRF02_AG, and subtype C strains of **HIV**-1 obtained from untreated patients from Vietnam, Cote d'Ivoire, and India were analyzed for their in vitro susceptibility to NRTIs, NNRTIs, PIs, and an entry inhibitor (T-20) using a recombinant viral assay (PHENOSCRIPT). The corresponding viruses, which had been previously sequenced in reverse transcriptase (RT), protease (prot), plus envelope (env) C2/V3 genes and had therefore been fully characterized, were further sequenced in env **HR1** + **HR2** regions. CRF01_AE isolates are sensitive to NRTIs and NNRTIs with the exception of one isolate that exhibits a decreased susceptibility to NNRTIs associated with a I135T substitution in RT. CRF02_AG and subtype C viruses are sensitive to NRTIs and NNRTIs but some CRF02_AG isolates tend to be resistant to abacavir, potentially related to associated substitutions of RT at positions 123 (D123N) plus 135 (I135V). Whereas all but one CRF01_AE isolates are fully susceptible to PIs, some CRF02_AG and, more frequently, some subtype C isolates are resistant to atazanavir. The role of substitutions in prot at positions of secondary resistance mutations 20, 36, 63, and 82 is raised with a potentially crucial role of the V82I substitution. Finally, all viruses tested, regardless of the CRF or subtype, are fully susceptible to T-20.

L19 ANSWER 6 OF 59 MEDLINE on STN

2006148916. PubMed ID: 16537590. Functional characterization of heptad repeat 1 and 2 mutants of the spike protein of severe acute respiratory syndrome coronavirus. Chan Woan-Eng; Chuang Chin-Kai; Yeh Shiou-Hwei; Chang Mau-Sun; Chen Steve S-L. (Institute of Biomedical Sciences, Academia Sinica, Nankang, Taipei 11529, Taiwan, Republic of China.) Journal of virology, (2006 Apr) Vol. 80, No. 7, pp. 3225-37. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB To understand the roles of heptad repeat 1(**HR1**) and **HR2** of the spike (S) protein of the severe acute respiratory syndrome coronavirus (SARS-CoV) in virus-cell interactions, the conserved Leu or Ile residues located at positions 913, 927, 941, and 955 in **HR1** and 1151, 1165, and 1179 in **HR2** were individually replaced with an alpha-helix-breaker Pro residue. The 913P mutant was expressed mainly as a faster-migrating, lower-molecular-weight S(L) form, while the wild type and all other mutants produced similar levels of both the S(L) form and the slower-migrating, higher-molecular-weight S(H) form. The wild-type S(L) form was processed to the S(H) form, whereas the S(L) form of the 913P mutant was inefficiently converted to the S(H) form after biosynthesis. None of these mutations affected cell surface expression or binding to its cognate ACE2 receptor. In a **human immunodeficiency virus** type 1/SARS S coexpression study, all mutants except the 913P mutant incorporated the S(H) form into the virions as effectively as did the wild-type S(H) form. The mutation at Ile-1151 did not affect membrane fusion or viral entry. The impaired viral entry of the 927P, 941P, 955P, and 1165P mutants was due to their inability to mediate membrane fusion, whereas the defect in viral entry of the 1179P mutant occurred not at the stage of membrane fusion but rather at a postfusion stage. Our study demonstrates the functional importance of **HR1** and **HR2** of the SARS-CoV spike protein in membrane fusion and viral entry.

L19 ANSWER 7 OF 59 MEDLINE on STN

2006148651. PubMed ID: 16464888. **HIV** entry inhibitors: mechanisms of action and resistance pathways. Briz Veronica; Poveda Eva; Soriano Vincent. (Department of Infectious Diseases, Hospital Carlos III, Calle Sinesio Delgado 10, Madrid, Spain.) The Journal of antimicrobial chemotherapy, (2006 Apr) Vol. 57, No. 4, pp. 619-27. Electronic Publication: 2006-02-07. Ref: 90. Journal code: 7513617. ISSN: 0305-7453. Pub. country: England: United Kingdom. Language: English.

AB Entry inhibitors represent a new generation of antivirals for the treatment of **HIV** infection. Several compounds which block the attachment of **HIV** gp120 to either the CD4 T cell receptor or the CCR5/CXCR4 co-receptors are currently in clinical development. Most of these compounds have different molecular structures and specific mechanisms of action. These agents are eagerly awaited by a growing number of patients carrying viruses resistant viruses to many of the current available reverse transcriptase and protease inhibitors. For enfuvirtide, the first and, so far, only entry inhibitor approved for clinical use, the main mechanism of resistance is the selection of changes within a 10 amino acid segment encompassing residues 36-45 within the **HR1** region of gp41. For other entry inhibitors, multiple changes in different gp120 domains (V1, V2, V3, C2 and C4) have been associated with loss of susceptibility to these agents, although in most cases with limited cross-resistance.

L19 ANSWER 8 OF 59 MEDLINE on STN

2006042244. PubMed ID: 16430194. Heptad-repeat-2 mutations enhance the stability of the enfuvirtide-resistant **HIV**-1 gp41 hairpin structure. Jenwitheesuk Ekachai; Samudrala Ram. (Department of Microbiology, University of Washington, School of Medicine, Seattle, WA 98195, USA.) Antiviral therapy, (2005) Vol. 10, No. 8, pp. 893-900. Journal code: 9815705. ISSN: 1359-6535. Pub. country: England: United Kingdom. Language: English.

AB Enfuvirtide (T20) is a peptide-based fusion inhibitor derived from the heptad repeat 2 (**HR2**) region of **HIV**-1 glycoprotein 41 (gp41). The inhibitor binds to the gp41 heptad repeat 1 (**HR1**) region, thereby blocking viral **HR1/HR2** association. Mutations in **HR1** have been reported to cause enfuvirtide resistance and reduce viral fitness. In this study, we first showed that scores obtained by a residue-specific all-atom probability discriminatory function (RAPDF) may be used as a reliable predictor of structural stability of gp41 mutants by comparing it to experimentally determined melting temperatures, and as a reliable indicator of enfuvirtide resistance by comparing it to experimentally determined fusion inhibition and viral fitness levels. We then generated an initial set of 28 theoretical structures of the **HR1/HR2** hairpin complex where each structure consists of one mutation on **HR1** known to cause enfuvirtide resistance and a wild-type amino acid at the corresponding **HR2** residue. Mutations were then introduced in the corresponding **HR2** residue of each structure where the wild-type amino acid was changed to each of the other nineteen amino acids. The enfuvirtide-resistant **HR1** mutants with compensatory mutations at the corresponding **HR2** residues had better RAPDF scores than those **HR1** mutants with wild-type **HR2**. This indicates that mutations in **HR2** improve structural stability of the **HR1/HR2** hairpin complex and may lead to enhanced enfuvirtide resistance when present with resistant **HR1** mutations. Modification of the amino acid side chains that contribute to enfuvirtide resistance using the RAPDF scores as a guide may help design of a second generation of fusion inhibitors against the enfuvirtide-resistant strains.

L19 ANSWER 9 OF 59 MEDLINE on STN

2005690425. PubMed ID: 16372284. Long-term monitoring of genotypic and phenotypic resistance to T20 in treated patients infected with **HIV**-1. Perez-Alvarez L; Carmona R; Ocampo A; Asorey A; Miralles C; Perez de

Castro S; Pinilla M; Contreras G; Taboada J A; Najera R. (Area de Patogenia Viral, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain.) Journal of medical virology, (2006 Feb) Vol. 78, No. 2, pp. 141-7. Journal code: 7705876. ISSN: 0146-6615. Pub. country: United States. Language: English.

AB The aim of this study was to investigate the susceptibility to T20 and the dynamics of amino acid changes in **HR1** and **HR2** of gp41 of **HIV**-1 obtained from plasma, peripheral blood mononuclear cells (PBMC), and primary isolates (PI) in four highly antiretroviral-experienced patients. These patients received T20 plus an antiretroviral regimen and were followed-up over a period of 40-72 weeks. In one non-responder patient, N43D substitution was detected at 12 weeks of treatment, in association with a value of T20-IC50 of 10 microg/ml (10-fold increase). Double mutations N42T + N43D were observed in plasma RNA at 32 weeks and remained detectable up to 16 weeks after the withdrawal of the drug. The S138A substitution in **HR2** was observed in plasma RNA at 32 weeks, and both in plasma RNA and in PI DNA at 40 weeks, associated with an increase of the T20-IC50 to 25 microg/ml (25-fold increase). Mutations V101G and E137K, not reported previously, were also observed in the **HR2** region. Whether these new substitutions play a role in T20 resistance needs to be examined. In three temporary responders, coinciding with viral load rebound, G36D, and N42T substitutions were observed at 12, 24, and 40 weeks. G36D mutation was associated with a value of T20-IC50 of 5 microg/ml. The **HR2** S138A mutation was detected after the detection of **HR1** substitutions and was associated with an increase in the level of T20-IC50 to 125 microg/ml (125-fold increase) All these data reinforce the role of gp41 amino acids 36-45 and the potential influence of the **HR2** S138A mutation in the genotypic/phenotypic resistance to T20.

L19 ANSWER 10 OF 59 MEDLINE on STN

2005671901. PubMed ID: 16290276. Why are **HIV**-1 fusion inhibitors not effective against SARS-CoV? Biophysical evaluation of molecular interactions. Veiga Salome; Yuan Yunyun; Li Xuqin; Santos Nuno C; Liu Gang; Castanho Miguel A R B. (Centro de Quimica e Bioquimica, Faculdade de Ciencias da Universidade de Lisboa, Campo Grande C8, 1749-016 Lisboa, Portugal.) Biochimica et biophysica acta, (2006 Jan) Vol. 1760, No. 1, pp. 55-61. Electronic Publication: 2005-10-28. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB The envelope spike (S) glycoprotein of the severe acute respiratory syndrome associated coronavirus (SARS-CoV) mediates the entry of the virus into target cells. Recent studies point out to a cell entry mechanism of this virus similar to other enveloped viruses, such as **HIV**-1. As it happens with other viruses peptidic fusion inhibitors, SARS-CoV S protein **HR2**-derived peptides are potential therapeutic drugs against the virus. It is believed that **HR2** peptides block the six-helix bundle formation, a key structure in the viral fusion, by interacting with the **HR1** region. It is a matter of discussion if the **HIV**-1 gp41 **HR2**-derived peptide T20 (enfuvirtide) could be a possible SARS-CoV inhibitor given the similarities between the two viruses. We tested the possibility of interaction between both T20 (**HIV**-1 gp41 **HR2**-derived peptide) and T-1249 with S protein **HR1**- and **HR2**-derived peptides. Our biophysical data show a significant interaction between a SARS-CoV **HR1**-derived peptide and T20. However, the interaction is only moderate (K(B)=(1.1+/-0.3)x10(5) M(-1)). This finding shows that the reasoning behind the hypothesis that T20, already approved for clinical application in AIDS treatment, could inhibit the fusion of SARS-CoV with target cells is correct but the effect may not be strong enough for application.

L19 ANSWER 11 OF 59 MEDLINE on STN

2005665310. PubMed ID: 16352560. Expanded tropism and altered activation of a retroviral glycoprotein resistant to an entry inhibitor peptide.

Amberg Sean M; Netter Robert C; Simmons Graham; Bates Paul. (Department of Microbiology, University of Pennsylvania School of Medicine, 225 Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA 19104-6076, USA.) Journal of virology, (2006 Jan) Vol. 80, No. 1, pp. 353-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The envelope of class I viruses can be a target for potent viral inhibitors, such as the **human immunodeficiency virus** type 1 (**HIV**-1) inhibitor enfuvirtide, which are derived from the C-terminal heptad repeat (**HR2**) of the transmembrane (TM) subunit. Resistance to an **HR2**-based peptide inhibitor of a model retrovirus, subgroup A of the Avian Sarcoma and Leukosis Virus genus (ASLV-A), was studied by examining mutants derived by viral passage in the presence of inhibitor. Variants with reduced sensitivity to inhibitor were readily selected in vitro. Sensitivity determinants were identified for 13 different isolates, all of which mapped to the TM subunit. These determinants were identified in two regions: (i) the N-terminal heptad repeat (**HR1**) and (ii) the N-terminal segment of TM, between the subunit cleavage site and the fusion peptide. The latter class of mutants identified a region outside of the predicted **HR2**-binding site that can significantly alter sensitivity to inhibitor. A subset of the **HR1** mutants displayed the unanticipated ability to infect nonavian cells. This expanded tropism was associated with increased efficiency of envelope triggering by soluble receptor at low temperatures, as measured by protease sensitivity of the surface subunit (SU) of envelope. In addition, expanded tropism was linked for the most readily triggered mutants with increased sensitivity to neutralization by SU-specific antiserum. These observations depict a class of **HR2** peptide-selected mutations with a reduced activation threshold, thereby allowing the utilization of alternative receptors for viral entry.

L19 ANSWER 12 OF 59 MEDLINE on STN

2005621192. PubMed ID: 16302461. Enfuvirtide, the first fusion inhibitor to treat **HIV** infection. Poveda Eva; Briz Veronica; Soriano Vincent. (Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain.) AIDS reviews, (2005 Jul-Sep) Vol. 7, No. 3, pp. 139-47. Ref: 71. Journal code: 101134876. ISSN: 1139-6121. Pub. country: Spain. Language: English.

AB Entry inhibitors are a new class of drugs for the treatment of **HIV** infection. Enfuvirtide is the first compound of this family to be approved for clinical use. It blocks **HIV** fusion to host cells. It is a synthetic peptide that mimics an **HR2** fragment of gp41, blocking the formation of a six-helix bundle structure which is critical in the fusion process. Enfuvirtide is a good therapeutic option as rescue therapy in combination with other active antiretrovirals and works against different **HIV**-1 variants, including all group M subtypes and group O. However, it is not active against **HIV**-2. The main mechanism of resistance to enfuvirtide depends of the selection of changes in a 10-amino acid domain between residues 36 to 45 in the **HR1** region of gp41. Single and double mutations in this region have been shown to result in high-level resistance to enfuvirtide. A negative impact of enfuvirtide-resistance mutations on viral fitness has been postulated, since resistance mutations tend to disappear soon after drug discontinuation and because immunologic benefits have been noticed despite virologic failure in patients undergoing enfuvirtide treatment.

L19 ANSWER 13 OF 59 MEDLINE on STN

2005617776. PubMed ID: 16253271. Design and characterization of viral polypeptide inhibitors targeting Newcastle disease virus fusion. Zhu Jieqing; Jiang Xiuli; Liu Yueyong; Tien Po; Gao George F. (Center For Molecular Virology, Institute of Microbiology, Chinese Academy of Sciences, Zhongguancun Beiyitiao, Beijing 100080, China.) Journal of molecular biology, (2005 Dec 2) Vol. 354, No. 3, pp. 601-13. Electronic Publication: 2005-10-10. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: England: United Kingdom. Language: English.

AB Paramyxovirus infections can be detected worldwide with some emerging zoonotic viruses and currently there are no specific therapeutic treatments or vaccines available for many of these diseases. Recent studies have demonstrated that peptides derived from the two heptad repeat regions (**HR1** and **HR2**) of paramyxovirus fusion proteins could be used as inhibitors of virus fusion. The mechanism underlying this activity is in accordance with that of class I virus fusion proteins, of which **human immunodeficiency virus** (**HIV**) and influenza virus fusion proteins are members. For class I virus fusion proteins, the **HR1** fragment binds to **HR2** to form a six-helix bundle with three **HR1** fragments forming the central coiled bundle surrounded by three coiled **HR2** fragments in the post fusion conformational state (fusion core). It is hypothesized that the introduced exogenous **HR1** or **HR2** can compete against their endogenous counterparts, which results in fusion inhibition. Using Newcastle disease virus (NDV) as a model, we designed several protein inhibitors, denoted HR212 as well asHR121 and 5-Helix, which could bind the **HR1** or **HR2** region of fusion protein, respectively. All the proteins were expressed and purified using a GST-fusion expression system in Escherichia coli. The HR212 or GST-HR212 protein, which binds the **HR1** peptide in vitro, displayed inhibitory activity against NDV-mediated cell fusion, while the HR121 and 5-Helix proteins, which bind the **HR2** peptide in vitro, inhibited virus fusion from the avirulent NDV strain when added before the cleavage of the fusion protein. These results showed that the designed HR212, HR121 or 5-Helix protein could serve as specific antiviral agents. These data provide additional insight into the difference between the virulent and avirulent strains of NDV.

L19 ANSWER 14 OF 59 MEDLINE on STN

2005606869. PubMed ID: 16286053. Dynamics of enfuvirtide resistance in **HIV**-infected patients during and after long-term enfuvirtide salvage therapy. Poveda Eva; Rodes Berta; Lebel-Binay Sophie; Faudon Jean-Louis; Jimenez Victoria; Soriano Vincent. (Department of Infectious Diseases, Hospital Carlos III, Madrid 28029, Spain.) Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, (2005 Dec) Vol. 34, No. 4, pp. 295-301. Journal code: 9815671. ISSN: 1386-6532. Pub. country: Netherlands. Language: English.

AB Enfuvirtide (ENF) is the first of a novel class of drugs that blocks **HIV** fusion to host cells. We analyzed the dynamics of genotypic and phenotypic resistance to ENF during and after long-term ENF therapy and its clinical implications in eight heavily treatment-experienced **HIV**-infected patients who underwent salvage therapy with enfuvirtide along with other antiretroviral agents. All patients showed a rapid decline in plasma **HIV**-RNA followed by viral rebound. Changes at codons 36, 42, 43 and/or 44 within the **HR1** region of gp41 were selected in all cases, resulting in high-level phenotypic resistance to ENF, ranging from 15- to 445-fold. Both genotypic and phenotypic resistance to ENF rapidly disappeared after discontinuation of the drug, suggesting that ENF-resistant viruses may have an impaired replicative capacity.

L19 ANSWER 15 OF 59 MEDLINE on STN

2005551218. PubMed ID: 16130177. Development of **HIV** fusion inhibitors. Schneider Stephen E; Bray Brian L; Mader Catherine J; Friedrich Paul E; Anderson Mark W; Taylor Tracy S; Boshernitzan Natalia; Niemi Toivo E; Fulcher Brian C; Whight Sheila R; White Jonathan M; Greene Reagan J; Stoltenberg Larry E; Lichty Maynard. (Process Research and Development, Trimeris, Inc., Durham, Morrisville, NC, USA.. sschneider@trimeris.com) . Journal of peptide science : an official publication of the European Peptide Society, (2005 Nov) Vol. 11, No. 11, pp. 744-53. Journal code: 9506309. ISSN: 1075-2617. Pub. country: England: United Kingdom. Language: English.

AB In the past 25 years, the worldwide AIDS epidemic has grown such that roughly 38 million people were estimated to be living with the disease

worldwide at the end of 2003. The introduction of antiretroviral-based therapies, beginning in 1987, has enabled many to live with **HIV** as a chronic, rather than terminal, disease. However, the emergence and spread of drug-resistant strains highlights the continued need for new therapies with novel modes of action. In 2003, the FDA and EMEA approved enfuvirtide (Fuzeon), a 36 amino acid peptide derived from the natural gp41 **HR2** sequence, as the first **HIV** fusion inhibitor. T-1249, a 39 amino acid fusion inhibitor, is active against viruses that develop resistance to enfuvirtide. The development of FIs and the processes to manufacture enfuvirtide and T-1249 on an unprecedented scale for peptide therapeutics are presented. Synthetic routes based on a combination of solid phase peptide synthesis and solution phase fragment condensation as well as the analytical controls necessary to insure a robust process are discussed.

L19 ANSWER 16 OF 59 MEDLINE on STN

2005544129. PubMed ID: 16203977. A human monoclonal antibody neutralizes diverse **HIV**-1 isolates by binding a critical gp41 epitope. Miller Michael D; Geleziunas Romas; Bianchi Elisabetta; Lennard Simon; Hrin Renee; Zhang Hangchun; Lu Meiqing; An Zhiqiang; Ingallinella Paolo; Finotto Marco; Mattu Marco; Finnefrock Adam C; Bramhill David; Cook James; Eckert Debra M; Hampton Richard; Patel Mayuri; Jarantow Stephen; Joyce Joseph; Ciliberto Gennaro; Cortese Riccardo; Lu Ping; Strohl William; Schleif William; McElhaugh Michael; Lane Steven; Lloyd Christopher; Lowe David; Osbourn Jane; Vaughan Tristan; Emini Emilio; Barbato Gaetano; Kim Peter S; Hazuda Daria J; Shiver John W; Pessi Antonello. (Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, USA.. michael_miller1@merck.com) . Proceedings of the National Academy of Sciences of the United States of America, (2005 Oct 11) Vol. 102, No. 41, pp. 14759-64. Electronic Publication: 2005-10-03. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB **HIV**-1 entry into cells is mediated by the envelope glycoprotein receptor-binding (gp120) and membrane fusion-promoting (gp41) subunits. The gp41 heptad repeat 1 (**HR1**) domain is the molecular target of the fusion-inhibitor drug enfuvirtide (T20). The **HR1** sequence is highly conserved and therefore considered an attractive target for vaccine development, but it is unknown whether antibodies can access **HR1**. Herein, we use gp41-based peptides to select a human antibody, 5H/I1-BMV-D5 (D5), that binds to **HR1** and inhibits the assembly of fusion intermediates in vitro. D5 inhibits the replication of diverse **HIV**-1 clinical isolates and therefore represents a previously unknown example of a crossneutralizing IgG selected by binding to designed antigens. NMR studies and functional analyses map the D5-binding site to a previously identified hydrophobic pocket situated in the **HR1** groove. This hydrophobic pocket was proposed as a drug target and subsequently identified as a common binding site for peptide and peptidomimetic fusion inhibitors. The finding that the D5 fusion-inhibitory antibody shares the same binding site suggests that the hydrophobic pocket is a "hot spot" for fusion inhibition and an ideal target on which to focus a vaccine-elicited antibody response. Our data provide a structural framework for the design of new immunogens and therapeutic antibodies with crossneutralizing potential.

L19 ANSWER 17 OF 59 MEDLINE on STN

2005513637. PubMed ID: 16186242. Selection of **human immunodeficiency virus** type 1 R5 variants with augmented replicative capacity and reduced sensitivity to entry inhibitors during severe immunodeficiency. Repits Johanna; Oberg Monica; Esbjornsson Joakim; Medstrand Patrik; Karlsson Anders; Albert Jan; Fenyo Eva Maria; Jansson Marianne. (Department of Laboratory Medicine, Division of Medical Microbiology, Lund University, Solvegatan 23, 223 62 Lund, Sweden.) The Journal of general virology,

(2005 Oct) Vol. 86, No. Pt 10, pp. 2859-69. Journal code: 0077340. ISSN: 0022-1317. Pub. country: England: United Kingdom. Language: English.

AB Early in **human immunodeficiency virus** 1 (**HIV**-1) infection CCR5-using (R5) viruses predominate. With disease progression, approximately 50% of infected individuals develop viruses able to use CXCR4. In the present work, the evolution of the biological properties of **HIV**-1 was studied in patients who retain viruses with an R5 phenotype despite AIDS onset. A panel of primary R5 **HIV**-1 isolates sequentially obtained at an asymptomatic stage and after AIDS diagnosis was examined. The viruses were selected based on our previous observation that R5 variants with reduced sensitivity to RANTES inhibition may appear during disease progression. Biological properties of the early and late R5 viruses, including infectivity, replicative capacity, impact of cationic polymer and sensitivity to inhibition by the entry inhibitors T-20 and TAK-779, were evaluated. R5 viruses isolated after AIDS onset displayed elevated replicative capacity and infectivity, and did not benefit from cationic polymer assistance during infection. Late R5 isolates also exhibited reduced sensitivity to inhibition by T-20 and TAK-779, even though the included patients were naive to treatment with entry inhibitors and the isolates had not acquired mutations within the gp41 **HR1** region. In addition, CD4+ T-cell counts at the time of R5 virus isolation correlated with infectivity, replicative capacity and sensitivity to inhibition by entry inhibitors. The results indicate that R5 **HIV**-1 variants with augmented replicative capacity and reduced sensitivity to entry inhibitors may be selected for during severe immunodeficiency. At a time when the clinical use of entry inhibitors is increasing, this observation could be of importance in the optimal design of such treatments.

L19 ANSWER 18 OF 59 MEDLINE on STN

2005434661. PubMed ID: 16103771. Effect of naturally-occurring gp41 **HR1** variations on susceptibility of **HIV**-1 to fusion inhibitors. Chinnadurai Raghavan; Munch Jan; Kirchhoff Frank. (Department of Virology, Universitatsklinikum, Ulm, Germany.) AIDS (London, England), (2005 Sep 2) Vol. 19, No. 13, pp. 1401-5. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Sequence variations in the gp41 heptad repeat 1 (**HR1**) region have been identified in some treatment-naive **HIV**-1-infected patients but it remained elusive whether they confer resistance to fusion inhibitors. OBJECTIVE: To evaluate whether naturally occurring sequence variations in the **HIV**-1 group M gp41 **HR1** region affect the sensitivity to inhibition by T-20 and T-1249. METHODS: Site-directed mutagenesis was used to generate **HIV**-1 NL4-3 mutants containing changes in the gp41 **HR1** domain which have been previously identified in treatment-naive patients infected with various **HIV**-1 group M subtypes. **HIV**-1 variants were produced by transient transfection of 293T cells and used to determine viral infectivity and sensitivity to the fusion inhibitors T-20 and T-1249. RESULTS: Most naturally occurring sequence variations in the **HR1** domain did not reduce viral infectivity. Three of the 10 **HIV**-1 variants analysed containing a single substitution of L33V, which is frequently present in subtype D isolates, or combined changes of L54M/Q56K or L34M/L54M/Q56R showed about fivefold reduced sensitivity to inhibition by T-20. In comparison, none of these **HR1** sequence variations conferred resistance to T-1249. CONCLUSION: Some naturally occurring sequence variations in the gp41 **HR1** region reduce sensitivity of **HIV**-1 to inhibition by T-20 but not T-1249.

L19 ANSWER 19 OF 59 MEDLINE on STN

2005393336. PubMed ID: 16051817. Determinants of **human immunodeficiency virus** type 1 resistance to membrane-anchored gp41-derived peptides. Lohrengel Sabine; Hermann Felix; Hagmann Isabel; Oberwinkler Heike; Scrivano Laura; Hoffmann Caroline; von Laer Dorothee;

Dittmar Matthias T. (Abt. Virologie, Hygiene-Institut, Universitat Heidelberg, D-69120 Heidelberg, Germany.) Journal of virology, (2005 Aug) Vol. 79, No. 16, pp. 10237-46. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The expression of a membrane-anchored gp41-derived peptide (M87) has been shown to confer protection from infection through **human immunodeficiency virus** type 1 (**HIV**-1) (Hildinger et al., J. Virol. 75:3038-3042, 2001). In an effort to characterize the mechanism of action of this membrane-anchored peptide in comparison to the soluble peptide T-20, we selected resistant variants of **HIV**-1(NL4-3) and **HIV**-1(BaL) by serial virus passage using PM1 cells stably expressing peptide M87. Sequence analysis of the resistant isolates showed different patterns of selected point mutations in heptad repeat regions 1 and 2 (**HR1** and **HR2**, respectively) for the two viruses analyzed. For **HIV**-1(NL4-3) a single amino acid change at position 33 in **HR1** (L33S) was selected, whereas for **HIV**-1(BaL) the majority of the sequences obtained showed two amino acid changes, one in **HR1** and one in **HR2** (I48V/N126K). In both selections the most important contiguous 3-amino-acid sequence, GIV, within **HR1**, associated with resistance to soluble T-20, was not changed. Site-directed mutagenesis studies confirmed the importance of the characterized point mutations to confer resistance to M87 as well as to soluble T-20 and T-649. Replication capacity and dual-color competition assays revealed that the double mutation I48V/N126K in **HIV**-1(BaL) results in a strong reduction of viral fitness, whereas the L33S mutation in **HIV**-1(NL4-3) did enhance viral fitness compared to the respective parental viruses. However, the selected point mutations did not confer resistance to the more recently described optimized membrane-anchored fusion inhibitor M87o (Egelhofer et al., J. Virol. 78:568-575, 2004), strengthening the importance of this novel antiviral concept for gene therapy approaches.

L19 ANSWER 20 OF 59 MEDLINE on STN

2005338444. PubMed ID: 15989465. Enfuvirtide is active against **HIV** type 1 group O. Poveda Eva; Barreiro Pablo; Rodes Berta; Soriano Vincent. (Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain.) AIDS research and human retroviruses, (2005 Jun) Vol. 21, No. 6, pp. 583-5. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB A high diversity within the **HR1/HR2** regions of viral gp41 and one natural change (N42D) within the 36-45 aa domain in **HIV**-1 group O in comparison with **HIV**-1 group M isolates have led us to suspect that enfuvirtide (ENF) should not be active against **HIV**-1 group O. We analyzed in vitro and in vivo the antiviral activity of ENF against **HIV**-1 group O isolates. The IC50 at baseline was 0.15 +/- 0.028 microg/ml in a clinically derived virus specimen. After initiating treatment with ENF, a significant decline in plasma **HIV**-RNA and CD4 gain was noticed in one patient. Therefore, individuals with **HIV**-1 group O strains might benefit from ENF therapy.

L19 ANSWER 21 OF 59 MEDLINE on STN

2005330572. PubMed ID: 15950253. An alternative conformation of the gp41 heptad repeat 1 region coiled coil exists in the **human immunodeficiency virus** (**HIV**-1) envelope glycoprotein precursor. Mische Claudia C; Yuan Wen; Strack Bettina; Craig Stewart; Farzan Michael; Sodroski Joseph. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, MA 02115, USA.) Virology, (2005 Jul 20) Vol. 338, No. 1, pp. 133-43. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB The **human immunodeficiency virus** (**HIV**-1) transmembrane envelope glycoprotein, gp41, which mediates virus-cell fusion, exists in at least three different conformations within the trimeric envelope glycoprotein complex. The structures of the prefusogenic and intermediate states are

unknown; structures representing the postfusion state have been solved. In the postfusion conformation, three helical heptad repeat 2 (**HR2**) regions pack in an antiparallel fashion into the hydrophobic grooves on the surface of a triple-helical coiled coil formed by the heptad repeat 1 (**HR1**) regions. We studied the prefusogenic conformation of gp41 by mutagenic alteration of membrane-anchored and soluble forms of the **HIV**-1 envelope glycoproteins. Our results indicate that, in the **HIV**-1 envelope glycoprotein precursor, the gp41 **HR1** region is in a conformation distinct from that of a trimeric coiled coil. Thus, the central gp41 coiled coil is formed during the transition of the **HIV**-1 envelope glycoproteins from the precursor state to the receptor-bound intermediate.

L19 ANSWER 22 OF 59 MEDLINE on STN

2005284642. PubMed ID: 15929708. Enfuvirtide binding domain is highly conserved in non-B **HIV** type 1 strains from Cameroon, West Central Africa. Aghokeng Avelin Fobang; Ewane Leonard; Awazi Bih; Nanfack Aubin; Delaporte Eric; Zekeng Leopold; Peeters Martine. (Laboratoire de Sante Hygiene Mobile, Yaounde, Cameroon.) AIDS research and human retroviruses, (2005 May) Vol. 21, No. 5, pp. 430-3. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Recently T-20 or enfuvirtide, the first drug of a new class of antiretrovirals targeting the entry stage of the virus life cycle, has been clinically approved. Enfuvirtide is a peptide derived from the **HR2** region of the transmembrane glycoprotein from the HXB2 **HIV**-1 subtype B prototype strain that binds to the **HR1** region. Drug resistance seems to occur in the **HR1** region between amino acids 36 and 45. We examined to what extent this region is conserved in 184 non-B strains from Cameroon: 132 (71.7%) CRF02-AG, 14 (7.6%) subtype A, 11 (5.9%) F2, 9 (4.8%) subtype D, 8 (4.3%) subtype G, 4 (2.1%) CRF01-AE, 4 (2.1%) CRF11-cpx, and 2 (1.1%) CRF06-cpx. Among the 184 strains studied, no amino acid mutation was found in the highly conserved three amino acid motif at codons 36-38 (GIV) that are important determinants of viral susceptibility to enfuvirtide. Other common substitutions like Q40H and N42T were also absent. The N42S polymorphism was present in 148 (80.4%) strains. Analysis of the **HR2** domain, from which the peptide is derived, indicated a much greater genetic variability as compared to **HR1**.

L19 ANSWER 23 OF 59 MEDLINE on STN

2005280239. PubMed ID: 15913557. Rational design of highly potent **HIV**-1 fusion inhibitory proteins: implication for developing antiviral therapeutics. Ni Ling; Gao George F; Tien Po. (Department of Molecular Virology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100080, PR China.) Biochemical and biophysical research communications, (2005 Jul 8) Vol. 332, No. 3, pp. 831-6. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Recombinant protein containing one heptad-repeat 1 (**HR1**) segment and one **HR2** segment of the **HIV**-1 gp41 (**HR1**-**HR2**) has been shown to fold into thermally stable six-helix bundle, representing the fusogenic core of gp41. In this study, we have used the fusogenic core as a scaffold to design **HIV**-1 fusion inhibitory proteins by linking another **HR1** to the C terminus of **HR1**-**HR2** (HR121) or additional **HR2** to the N terminus of **HR1**-**HR2** (HR212). Both recombinant proteins could be abundantly and solubly expressed and easily purified, exhibiting high stability and potent inhibitory activity on **HIV**-1 fusion with IC50 values of 16.2+/-2.8 and 2.8+/-0.63 nM, respectively. These suggest that these rationally designed proteins can be further developed as novel anti-**HIV**-1 therapeutics.

L19 ANSWER 24 OF 59 MEDLINE on STN

2005163352. PubMed ID: 15795284. Enfuvirtide resistance mutations: impact on **human immunodeficiency virus** envelope function, entry inhibitor

sensitivity, and virus neutralization. Reeves Jacqueline D; Lee Fang-Hua; Miamidian John L; Jabara Cassandra B; Juntilla Marisa M; Doms Robert W. (Department of Microbiology, University of Pennsylvania, 225 Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA 19104, USA.. jreeves@mail.med.upenn.edu) . Journal of virology, (2005 Apr) Vol. 79, No. 8, pp. 4991-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Enfuvirtide (ENF/T-20/Fuzeon), the first **human immunodeficiency virus** (**HIV**) entry inhibitor to be licensed, targets a structural intermediate of the entry process. ENF binds the **HR1** domain in gp41 after Env has bound CD4, preventing conformational changes needed for membrane fusion. Mutations in **HR1** that confer ENF resistance can arise following ENF therapy. ENF resistance mutations were introduced into an R5- and X4-tropic Env to examine their impact on fusion, infection, and sensitivity to different classes of entry inhibitors and neutralizing antibodies. **HR1** mutations could reduce infection and fusion efficiency and also delay fusion kinetics, likely accounting for their negative impact on viral fitness. **HR1** mutations had minimal effect on virus sensitivity to other classes of entry inhibitors, including those targeting CD4 binding (BMS-806 and a CD4-specific monoclonal antibody [MAb]), coreceptor binding (CXCR4 inhibitor AMD3100 and CCR5 inhibitor TAK-779), or fusion (T-1249), indicating that ENF-resistant viruses can remain sensitive to other entry inhibitors in vivo. Some **HR1** mutations conferred increased sensitivity to a subset of neutralizing MAbs that likely target fusion intermediates or with epitopes preferentially exposed following receptor interactions (17b, 48D, 2F5, 4E10, and IgGb12), as well as sera from some **HIV**-positive individuals. Mechanistically, enhanced neutralization correlated with reduced fusion kinetics, indicating that, in addition to steric constraints, kinetics may also limit virus neutralization by some antibodies. Therefore, escape from ENF comes at a cost to viral fitness and may confer enhanced sensitivity to humoral immunity due to prolonged exposure of epitopes that are not readily accessible in the native Env trimer. Resistance to other entry inhibitors was not observed.

L19 ANSWER 25 OF 59 MEDLINE on STN

2005148320. PubMed ID: 15781229. Design of recombinant protein-based SARS-CoV entry inhibitors targeting the heptad-repeat regions of the spike protein S2 domain. Ni Ling; Zhu Jieqing; Zhang Junjie; Yan Meng; Gao George F; Tien Po. (Department of Molecular Virology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100080, PR China.) Biochemical and biophysical research communications, (2005 Apr 29) Vol. 330, No. 1, pp. 39-45. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Entry of SARS-CoV into a target cell is initiated by binding of the S1 domain of spike protein to a receptor, followed by conformational changes of the spike protein S2 domain, resulting in the formation of a six-helix bundle by the heptad-repeat (**HR1** and **HR2**) regions. Our previous studies have demonstrated that peptides derived from **HR2** region could inhibit SARS-CoV entry. However, synthesis of these peptides is at high cost. In this study, we designed two recombinant proteins, one containing two **HR1** and one **HR2** peptides (denoted HR121), and the other consisting of two **HR2** and one **HR1** peptides (designated HR212). These two proteins could be easily purified with the low cost of production, exhibiting high stability and potent inhibitory activity on entry of the **HIV**/SARS pseudoviruses with IC(50) values of 4.13 and 0.95muM, respectively. These features suggest that HR121 and HR212 can serve as potent inhibitors of SARS-CoV entry.

L19 ANSWER 26 OF 59 MEDLINE on STN

2005141020. PubMed ID: 15735441. Depletion in antibodies targeted to the **HR2** region of **HIV**-1 glycoprotein gp41 in sera of **HIV**-1-seropositive

patients treated with T20. Vincent Nadine; Tardy Jean-Claude; Livrozet Jean-Michel; Lucht Frederic; Fresard Anne; Genin Christian; Malvoisin Etienne. (Groupe Immunite des Muqueuses et Agents Pathogenes, Faculty of Medicine of Saint-Etienne, France.) Journal of acquired immune deficiency syndromes (1999), (2005 Mar 1) Vol. 38, No. 3, pp. 254-62. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB The anti-**HIV** drug T20 is a synthetic peptide derived from the **HR2** region of **HIV**-1 gp41. T20 contains the sequence ELDKWA, which binds the broadly neutralizing antibody 2F5. Using plates coated with T20 or with synthetic peptides and recombinant proteins representing gp120 or gp41 domains, this study investigated by enzyme-linked immunosorbent assay the levels of antibodies directed to the gp160 molecule in patients treated with T20. Analysis of sera obtained before and after administration of T20 indicated that the levels of antibodies directed to T20, to MBP44, a maltose binding protein representing the **HR2** region, and to 4765, a synthetic peptide containing the sequence ELDKWA, fell following administration of T20, while the levels of antibodies directed to other regions of gp41 ectodomain and to gp120 remained stable. The decline observed was independent of the viral load and of the total IgG concentration. Follow-up studies with sera obtained from **HIV**-1-seropositive patients naive to T20 indicated no decline in the level of antibodies directed to **HR2** and other regions of gp160. Analysis of sera obtained from a patient after 2 months of T20 treatment interruption showed a level of antibodies to the **HR2** region similar to that measured before administration of T20. The addition of increasing amounts of T20 to sera from T20-naive patients decreased the level of serum antibodies against peptide 4765, T20, and MBP44. The observation of antibody depletion by T20 suggests that anti-gp41 antibodies may interfere with T20 treatment by forming T20-antibody complexes.

L19 ANSWER 27 OF 59 MEDLINE on STN

2005112034. PubMed ID: 15742549. [Enfuvirtide, first fusion inhibitor in the treatment of **human immunodeficiency virus** infection: mechanism of action and pharmacokinetics]. Enfuvirtide, premier inhibiteur de fusion dans le traitement de l'infection par le virus de l'immunodeficience humaine: mecanisme d'action et pharmacocinetique. Raffi Francois. (Service des maladies infectieuses et tropicales, Hotel-Dieu CHU, place Alexis-Ricordeau, 44093 Nantes cedex 1, France.. francois.raffi@chu-nantes.fr) . Medecine et maladies infectieuses, (2004 Sep) Vol. 34 Spec No 1, pp. 3-7. Ref: 4. Journal code: 0311416. ISSN: 0399-077X. Pub. country: France. Language: French.

AB Enfuvirtide is a 36 amino-acid synthetic peptide derived from the **HR2** sequence of the **HIV**-1 gp41. Enfuvirtide is different from other antiretroviral drugs by its extra-cellular action where it binds to the **HR1** domain at the viral surface of the gp41. The drug inhibits the conformational change of the glycoprotein, preventing the intimate fusion between the **HIV** envelope and the CD4 cell membrane and finally the penetration of the viral capside into the target cells. Following a 90 mg subcutaneous injection, the plasma concentration rises rapidly to reach a 4.59 +/- 1.5 microg/ml Cmax between 5 and 7 hours. Residual concentrations are between 2.6 and 3.4 microg/ml and the bioavailability of the drug is approximately 80%. Plasma concentrations and area under curve are dose-dependant. The site of injection does not influence the pharmacokinetic parameters of the drug. Infuvirtide is not an inhibitor of the P450 cytochrome and no pharmacokinetic interactions have been reported with P450 metabolised drugs.

L19 ANSWER 28 OF 59 MEDLINE on STN

2005109324. PubMed ID: 15739619. Current status of anti-SARS agents. Shigeta Shiro; Yamase Toshihiro. (Department of Microbiology, Fukushima Medical University, School of Medicine, Fukushima, Japan..

sshingeta@fmu.ac.jp) . Antiviral chemistry chemotherapy, (2005) Vol. 16, No. 1, pp. 23-31. Ref: 48. Journal code: 9009212. ISSN: 0956-3202. Pub. country: England: United Kingdom. Language: English.

AB Severe acute respiratory syndrome (SARS) is a disease that has newly emerged in the 21st century, and is both severe and highly contagious. SARS first surfaced in late 2002 and spread within a few months from its origin in Guandong province, China, to more than 30 countries (World Health Organization, 2003). In this review, several antiviral substances shown to be active in vitro will be introduced and summarized in the order of the virus' replication steps; that is, binding to cellular receptor, fusion and entry to the cells, viral RNA replication and transcription, protein processing and so on. The possible clinical use of several synthetic peptides, including those that mimic the S-binding domain, the **HR2** fusion protein and SARS proteinase substrates, will be discussed. Monoclonal antibodies (Mabs) and established drugs, such as interferons and **HIV** proteinase inhibitors, are also discussed in relation to anti-SARS clinical use.

L19 ANSWER 29 OF 59 MEDLINE on STN

2005106747. PubMed ID: 15737628. Characterization of BIV Env core: implication for mechanism of BIV-mediated cell fusion. Li Shu; Zhu Jieqing; Peng Yu; Cui Shanshan; Wang Chunping; Gao George F; Tien Po. (Modern Virology Research Center, State Key Laboratory of Virology, College of Life Sciences, Wuhan University, Wuhan 430072, China.) Biochemical and biophysical research communications, (2005 Apr 8) Vol. 329, No. 2, pp. 603-9. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Entry of lentiviruses, such as **human immunodeficiency virus** type 1 (**HIV**-1) and simian immunodeficiency virus (SIV), requires folding of two heptad repeat regions (**HR1** and **HR2**) of gp41 into a trimer-of-hairpins, which subsequently brings virus and cell membrane into fusion. This motif is a generalized feature of viral fusion proteins and has been exploited in generating antiviral fusion agents. In the present paper, we report structural characters of Env protein from another lentivirus, bovine immunodeficiency virus (BIV), which contributes to a good animal model of **HIV**. BIV **HR1** and **HR2** regions are predicted by two different programs and expressed separately or conjointly in Escherichia coli. Biochemical and biophysical analyses show that the predicted HRs of BIV Env can form a stable trimer-of-hairpins or six-helix bundle just like that formed by feline immunodeficiency virus Env. Cell fusion assay demonstrates that the **HR2** peptide of BIV can efficiently inhibit the virus-mediated cell fusion.

L19 ANSWER 30 OF 59 MEDLINE on STN

2005097527. PubMed ID: 15728911. Emergence and evolution of enfuvirtide resistance following long-term therapy involves heptad repeat 2 mutations within gp41. Xu L; Pozniak A; Wildfire A; Stanfield-Oakley S A; Mosier S M; Ratcliffe D; Workman J; Joall A; Myers R; Smit E; Cane P A; Greenberg M L; Pillay D. (Health Protection Agency Antiviral Suspectibility Reference Unit, Birmingham, UK.) Antimicrobial agents and chemotherapy, (2005 Mar) Vol. 49, No. 3, pp. 1113-9. Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB The objective of this study was to track the evolution of sequence changes in both the heptad region 1 (**HR1**) and **HR2** domains of gp41 associated with resistance to enfuvirtide (ENF) in a patient cohort receiving long-term ENF treatment. We studied 17 highly antiretroviral agent-experienced patients receiving long-term ENF treatment with virological rebound or a lack of suppression. Sixty-two samples obtained after between 5 and 107 weeks of ENF therapy were analyzed. Baseline samples from 15 of these 17 patients were available for analysis. Viruses from five samples from four patients were also sequenced after the cessation of ENF therapy. Drug susceptibilities were assessed by a

pseudotype virus reporter assay. We identified **HR1** and **HR2** sequence changes over time in relation to the baseline sequences. Mutations in **HR1** (amino acids 36 to 45) were noted in all cases, including previously unreported changes N42Q/H and N43Q. In addition to a range of **HR2** sequence changes at polymorphic sites, isolates from 6 of 17 (35%) patients developed an S138A substitution in the **HR2** domain at least 8 weeks after the start of ENF treatment and also subsequent to the first emergence of **HR1** mutations. In most, but not all, cases the S138A mutation accompanied **HR1** mutations at position 43. Molecular modeling demonstrates the close proximity of S138A with amino acids 40 and 45 in **HR1**. Of note, isolates in samples available from four patients demonstrated the loss of both the **HR1** and the S138A **HR2** mutations following the cessation of therapy. We show that the S138A **HR2** mutation increased the level of resistance by approximately threefold over that conferred by the **HR1** mutation N43D. Continual evolution of **HR1** in the domain from amino acids 36 to 45 was observed during long-term ENF therapy. We have identified, for the first time, an ENF resistance-associated **HR2** mutation, S138A, which appeared in isolates from 6 of 17 patients with virological failure and demonstrated its potential to contribute to drug resistance. We propose that this represents a possible secondary and/or compensatory mutation, particularly when it coexists with mutations at position 43 in HR-1.

L19 ANSWER 31 OF 59 MEDLINE on STN

2005092124. PubMed ID: 15722032. Natural resistance-associated mutations to Enfuvirtide (T20) and polymorphisms in the gp41 region of different **HIV**-1 genetic forms from T20 naive patients. Carmona R; Perez-Alvarez L; Munoz M; Casado G; Delgado E; Sierra M; Thomson M; Vega Y; Vazquez de Parga E; Contreras G; Medrano L; Najera R. (Area de Patogenia Viral, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Majadahonda, 28220 Madrid, Spain.) Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, (2005 Mar) Vol. 32, No. 3, pp. 248-53. Journal code: 9815671. ISSN: 1386-6532. Pub. country: Netherlands. Language: English.

AB BACKGROUND: The natural occurrence of primary resistance mutations in reverse transcriptase (RT) and protease (PR) genes of **HIV**-1 isolates from untreated patients has been reported and it may have important implications for the response to drug treatment. It is predictable that the same occurs in the **HR1** region of gp41 sequence from patients who have never received T20 therapy, and in this regard it would be important to know not only the mutation frequencies at **HR1** region but also the natural polymorphisms at resistance-associated positions present in the absence of this drug. OBJECTIVES: The objectives of this study are to investigate the existence of natural resistance-associated mutations to T20 in **HR1** gp41 region corresponding to different **HIV**-1 genetic forms from T20 naive patients and to determine their prevalence. STUDY DESIGN: Two hundred **HIV**-1 gp41 sequences were included: subtype B: 164 (81.3%); subtype A: 15 (8.2%); subtype G: 10 (4.6%); subtype F: 6 (3.5%); subtype C: 3 (1.8%); subtype K: 1 (0.6%); and subtype D: 1 (0.6%). We analyzed the resistance-associated mutations previously described: Q32H/R, G36D/S, I37V, V38A/M, Q39R/H, Q40H, N42T/D/Q/H, N43D/S/K/Q, L44M, L45M, R46M and V69I. RESULTS: Natural resistance mutations to T20 were found at a high frequency: 10.5%, corresponding to 9.1% in subtype B and 16.7% in non-B subtype samples. Polymorphisms were more frequent in non-B and recombinant forms than in subtype B ($p<0.001$). Different substitutions were related to subtypes: N42S in subtypes A, B, G and C, but not in F, Q56R in subtype A from CRF02_AG, and L54M in subtype B from CRF14_BG. CONCLUSIONS: To our knowledge this is the first study describing natural-resistance to T20 among different **HIV**-1 subtypes, warranting a study of the biological significance of this mutations and their clinical relevance. The detection of differences between subtypes may have an influence on the rate and patterns of resistance in patients undergoing

T20 treatment.

L19 ANSWER 32 OF 59 MEDLINE on STN
2005023927. PubMed ID: 15650199. Identification of the membrane-active regions of the severe acute respiratory syndrome coronavirus spike membrane glycoprotein using a 16/18-mer peptide scan: implications for the viral fusion mechanism. Guillen Jaime; Perez-Berna Ana J; Moreno Miguel R; Villalain Jose. (Instituto de Biologia Molecular y Celular, Universidad Miguel Hernandez, E-03202 Elche-Alicante, Spain.) Journal of virology, (2005 Feb) Vol. 79, No. 3, pp. 1743-52. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.
AB We have identified the membrane-active regions of the severe acute respiratory syndrome coronavirus (SARS CoV) spike glycoprotein by determining the effect on model membrane integrity of a 16/18-mer SARS CoV spike glycoprotein peptide library. By monitoring the effect of this peptide library on membrane leakage in model membranes, we have identified three regions on the SARS CoV spike glycoprotein with membrane-interacting capabilities: region 1, located immediately upstream of heptad repeat 1 (**HR1**) and suggested to be the fusion peptide; region 2, located between **HR1** and **HR2**, which would be analogous to the loop domain of **human immunodeficiency virus** type 1; and region 3, which would correspond to the pretransmembrane region. The identification of these membrane-active regions, which are capable of modifying the biophysical properties of phospholipid membranes, supports their direct role in SARS CoV-mediated membrane fusion, as well as facilitating the future development of SARS CoV entry inhibitors.

L19 ANSWER 33 OF 59 MEDLINE on STN
2004606996. PubMed ID: 15345712. Crystal structure of severe acute respiratory syndrome coronavirus spike protein fusion core. Xu Yanhui; Lou Zhiyong; Liu Yiwei; Pang Hai; Tien Po; Gao George F; Rao Zihe. (Laboratory of Structural Biology, Tsinghua University, Beijing 100084 and National Laboratory of Bio-Macromolecules, Institute of Biophysics, Beijing 100101, China.) The Journal of biological chemistry, (2004 Nov 19) Vol. 279, No. 47, pp. 49414-9. Electronic Publication: 2004-09-01. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Severe acute respiratory syndrome coronavirus is a newly emergent virus responsible for a recent outbreak of an atypical pneumonia. The coronavirus spike protein, an enveloped glycoprotein essential for viral entry, belongs to the class I fusion proteins and is characterized by the presence of two heptad repeat (HR) regions, **HR1** and **HR2**. These two regions are understood to form a fusion-active conformation similar to those of other typical viral fusion proteins. This hairpin structure likely juxtaposes the viral and cellular membranes, thus facilitating membrane fusion and subsequent viral entry. The fusion core protein of severe acute respiratory syndrome coronavirus spike protein was crystallized, and the structure was determined at 2.8 A of resolution. The fusion core is a six-helix bundle with three **HR2** helices packed against the hydrophobic grooves on the surface of central coiled coil formed by three parallel **HR1** helices in an oblique antiparallel manner. This structure shares significant similarity with the fusion core structure of mouse hepatitis virus spike protein and other viral fusion proteins, suggesting a conserved mechanism of membrane fusion. Drug discovery strategies aimed at inhibiting viral entry by blocking hairpin formation, which have been successfully used in **human immunodeficiency virus** 1 inhibitor development, may be applicable to the inhibition of severe acute respiratory syndrome coronavirus on the basis of structural information provided here. The relatively deep grooves on the surface of the central coiled coil will be a good target site for the design of viral fusion inhibitors.

L19 ANSWER 34 OF 59 MEDLINE on STN

2004571046. PubMed ID: 15518555. Characterization of the heptad repeat regions, **HR1** and **HR2**, and design of a fusion core structure model of the spike protein from severe acute respiratory syndrome (SARS) coronavirus. Xu Yanhui; Zhu Jieqing; Liu Yiwei; Lou Zhiyong; Yuan Fang; Liu Yueyong; Cole David K; Ni Ling; Su Nan; Qin Lan; Li Xu; Bai Zhihong; Bell John I; Pang Hai; Tien Po; Gao George F; Rao Zihe. (Laboratory of Structural Biology, Tsinghua University, Beijing 100084, China.) Biochemistry, (2004 Nov 9) Vol. 43, No. 44, pp. 14064-71. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB Severe acute respiratory syndrome coronavirus (SARS-CoV) is a newly emergent virus responsible for a worldwide epidemic in 2003. The coronavirus spike proteins belong to class I fusion proteins, and are characterized by the existence of two heptad repeat (HR) regions, **HR1** and **HR2**. The **HR1** region in coronaviruses is predicted to be considerably longer than that in other type I virus fusion proteins. Therefore the exact binding sequence to **HR2** from the **HR1** is not clear. In this study, we defined the region of **HR1** that binds to **HR2** by a series of biochemical and biophysical measures. Subsequently the defined **HR1** (902-952) and **HR2** (1145-1184) chains, which are different from previously defined binding regions, were linked together by a flexible linker to form a single-chain construct, 2-Helix. This protein was expressed in Escherichia coli and forms a typical six-helix coiled coil bundle. Highly conserved HR regions between mouse hepatitis virus (MHV) and SARS-CoV spike proteins suggest a similar three-dimensional structure for the two fusion cores. Here, we constructed a homology model for SARS coronavirus fusion core based on our biochemical analysis and determined the MHV fusion core structure. We also propose an important target site for fusion inhibitor design and several strategies, which have been successfully used in fusion inhibitor design for **human immunodeficiency virus** (**HIV**), for the treatment of SARS infection.

L19 ANSWER 35 OF 59 MEDLINE on STN

2004536660. PubMed ID: 15507629. Emergence of a drug-dependent **human immunodeficiency virus** type 1 variant during therapy with the T20 fusion inhibitor. Baldwin Chris E; Sanders Rogier W; Deng Yiqun; Jurriaans Suzanne; Lange Joep M; Lu Min; Berkhout Ben. (Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.) Journal of virology, (2004 Nov) Vol. 78, No. 22, pp. 12428-37. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The fusion inhibitor T20 belongs to a new class of anti-**human immunodeficiency virus** type 1 (**HIV**-1) drugs designed to block entry of the virus into the host cell. However, the success of T20 has met with the inevitable emergence of drug-resistant **HIV**-1 variants. We describe an evolutionary pathway taken by **HIV**-1 to escape from the selective pressure of T20 in a treated patient. Besides the appearance of T20-resistant variants, we report for the first time the emergence of drug-dependent viruses with mutations in both the **HR1** and **HR2** domains of envelope glycoprotein 41. We propose a mechanistic model for the dependence of **HIV**-1 entry on the T20 peptide. The T20-dependent mutant is more prone to undergo the conformational switch that results in the formation of the fusogenic six-helix bundle structure in gp41. A premature switch will generate nonfunctional envelope glycoproteins (dead spikes) on the surface of the virion, and T20 prevents this abortive event by acting as a safety pin that preserves an earlier prefusion conformation.

L19 ANSWER 36 OF 59 MEDLINE on STN

2004428959. PubMed ID: 15334539. **HIV** fusion and its inhibition in antiretroviral therapy. Greenberg Michael; Cammack Nick; Salgo Miklos; Smiley Lynn. (Trimeris Inc., Durham, NC 27707, USA.. MGreenberg@trimeris.com) . Reviews in medical virology, (2004 Sep-Oct)

Vol. 14, No. 5, pp. 321-37. Ref: 109. Journal code: 9112448. ISSN: 1052-9276. Pub. country: England: United Kingdom. Language: English.

AB The end of the twentieth century saw dramatic improvements in the prognosis of **HIV** infection brought about by the introduction of new agents (the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors) and their use in highly active combinations. However, the durability of these combination treatments is limited by a number of factors including adverse effects and extensive intra-class cross-resistance so that new antiretrovirals acting on alternative targets and having improved systemic tolerability profiles are required. The **HIV** binding and entry process offers several potential targets for antiviral interaction. These include gp120 binding to CD4 and to chemokine co-receptor molecules as well as the fusion process itself, which involves interactions between two leucine zipper-like 4-3 repeat regions within gp41 known as heptad repeat (HR)1 and **HR2**. Peptides such as enfuvirtide (formerly DP178 or T-20), that mimic the **HR2** region of gp41, inhibit **HIV**-1 by a mechanism that is thought to involve competitive binding to **HR1**. This review summarises the clinical development of enfuvirtide, providing an overview of the pharmacokinetic, efficacy and safety data in various patient populations, and also considers the evidence for the key role of genotypic changes in the **HR1** region (amino acids 36-45) in determining viral susceptibility to inhibition by enfuvirtide.

L19 ANSWER 37 OF 59 MEDLINE on STN

2004355455. PubMed ID: 15258964. Evolution of genotypic and phenotypic resistance to Enfuvirtide in **HIV**-infected patients experiencing prolonged virologic failure. Poveda Eva; Rodes Berta; Labernardiere Jean-Louis; Benito Jose Miguel; Toro Carlos; Gonzalez-Lahoz Juan; Faudon Jean-Louis; Clavel Francois; Schapiro Jonathan; Soriano Vincent. (Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain.) Journal of medical virology, (2004 Sep) Vol. 74, No. 1, pp. 21-8. Journal code: 7705876. ISSN: 0146-6615. Pub. country: United States. Language: English.

AB Four heavily antiretroviral-experienced **HIV**-infected patients had significant plasma **HIV**-RNA reductions (>1 log) after beginning an Enfuvirtide (ENF)-based rescue regimen. However, all had viral rebound shortly thereafter, sustaining high levels of plasma viremia over 80 weeks. These patients developed rapidly genotypic and phenotypic resistance to ENF. Mutations within the **HR1** env region were selected (N43D in three and G36V/D in one), resulting in high-level phenotypic resistance to ENF. Interestingly, two patients had a sustained CD4+ T-cell increase and two maintained stable CD4+ T-cell counts despite virologic failure under ENF. The possible mechanisms involved in this response were examined. Changes in virus tropism from R5 to R5/X4 were observed in two patients, in parallel with increases in ENF phenotypic resistance. Low levels of T-cell activation, T-cell turnover, and cytotoxic T lymphocyte (CTL) activity were found in all four patients. An overall increase in the proportion of viruses released from cells of the macrophage lineage was observed. In summary, single mutations at the **HR1** env region result in significant loss of susceptibility to ENF. Despite virologic failure, these patients may maintain elevated CD4+ counts through a reduction in their overall immune activation.

L19 ANSWER 38 OF 59 MEDLINE on STN

2004343395. PubMed ID: 15123674. Structural basis for coronavirus-mediated membrane fusion. Crystal structure of mouse hepatitis virus spike protein fusion core. Xu Yanhui; Liu Yiwei; Lou Zhiyong; Qin Lan; Li Xu; Bai Zhihong; Pang Hai; Tien Po; Gao George F; Rao Zihe. (Laboratory of Structural Biology, Tsinghua University, Beijing 100084, China.) The Journal of biological chemistry, (2004 Jul 16) Vol. 279, No. 29, pp. 30514-22. Electronic Publication: 2004-04-27. Journal code: 2985121R.

ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The surface transmembrane glycoprotein is responsible for mediating virion attachment to cell and subsequent virus-cell membrane fusion. However, the molecular mechanisms for the viral entry of coronaviruses remain poorly understood. The crystal structure of the fusion core of mouse hepatitis virus S protein, which represents the first fusion core structure of any coronavirus, reveals a central hydrophobic coiled coil trimer surrounded by three helices in an oblique, antiparallel manner. This structure shares significant similarity with both the low pH-induced conformation of influenza hemagglutinin and fusion core of **HIV** gp41, indicating that the structure represents a fusion-active state formed after several conformational changes. Our results also indicate that the mechanisms for the viral fusion of coronaviruses are similar to those of influenza virus and **HIV**. The coiled coil structure has unique features, which are different from other viral fusion cores. Highly conserved heptad repeat 1 (**HR1**) and **HR2** regions in coronavirus spike proteins indicate a similar three-dimensional structure among these fusion cores and common mechanisms for the viral fusion. We have proposed the binding regions of **HR1** and **HR2** of other coronaviruses and a structure model of their fusion core based on our mouse hepatitis virus fusion core structure and sequence alignment. Drug discovery strategies aimed at inhibiting viral entry by blocking hairpin formation may be applied to the inhibition of a number of emerging infectious diseases, including severe acute respiratory syndrome.

L19 ANSWER 39 OF 59 MEDLINE on STN

2004287732. PubMed ID: 15161975. Structural characterization of the fusion-active complex of severe acute respiratory syndrome (SARS) coronavirus. Ingallinella Paolo; Bianchi Elisabetta; Finotto Marco; Cantoni Giovanna; Eckert Debra M; Supekar Vinit M; Bruckmann Chiara; Carfi Andrea; Pessi Antonello. (Istituto di Ricerche di Biologia Molecolare P. Angeletti, Via Pontina Km 30.600, 00040 Pomezia, Italy.) Proceedings of the National Academy of Sciences of the United States of America, (2004 Jun 8) Vol. 101, No. 23, pp. 8709-14. Electronic Publication: 2004-05-25. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The causative agent of a recent outbreak of an atypical pneumonia, known as severe acute respiratory syndrome (SARS), has been identified as a coronavirus (CoV) not belonging to any of the previously identified groups. Fusion of coronaviruses with the host cell is mediated by the envelope spike protein. Two regions within the spike protein of SARS-CoV have been identified, showing a high degree of sequence conservation with the other CoV, which are characterized by the presence of heptad repeats (**HR1** and **HR2**). By using synthetic and recombinant peptides corresponding to the **HR1** and **HR2** regions, we were able to characterize the fusion-active complex formed by this novel CoV by CD, native PAGE, proteolysis protection analysis, and size-exclusion chromatography. **HR1** and **HR2** of SARS-CoV associate into an antiparallel six-helix bundle, with structural features typical of the other known class I fusion proteins. We have also mapped the specific boundaries of the region, within the longer **HR1** domain, making contact with the shorter **HR2** domain. Notably, the inner **HR1** coiled coil is a stable alpha-helical domain even in the absence of interaction with the **HR2** region. Inhibitors binding to HR regions of fusion proteins have been shown to be efficacious against many viruses, notably **HIV**. Our results may help in the design of anti-SARS therapeutics.

L19 ANSWER 40 OF 59 MEDLINE on STN

2004285974. PubMed ID: 15186521. Sensitivity of **HIV** type 1 subtype C isolates to the entry inhibitor T-20. Cilliers Tonie; Patience Trudy; Pillay Candice; Papathanasopoulos Maria; Morris Lynn. (AIDS Virus Research Unit, National Institute for Communicable Diseases, Johannesburg, South

Africa.) AIDS research and human retroviruses, (2004 May) Vol. 20, No. 5, pp. 477-82. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB T-20 is the first in a new class of antiretroviral drugs targeting the entry stage of the virus life cycle. It is a 36 amino acid peptide that binds to the **HR1** region of gp41 preventing gp41-mediated fusion with the host cell membrane. T-20 was designed based on the **HR2** sequence of **HIV**-1 subtype B gp41, a region that shows significant genetic variation with **HIV**-1 subtype C sequences. In order to assess the efficacy of T-20 to inhibit subtype C isolates, a total of 23 isolates were tested for their ability to replicate in the presence of T-20. This included 15 isolates that used CCR5, five that used both CCR5 and CXCR4, and three that used CXCR4. Five of these were from patients failing other antiretroviral therapies. Sequence analysis of the **HR2** region indicated that there were 10-16 amino acid changes in the region corresponding to T-20. However, all isolates were effectively inhibited by T-20 at 1 microg/ml. There were no significant differences between viruses that used CCR5 or CXCR4 to enter cells. All isolates, except one, had GIV at positions 36-38 in the **HR1** region. One isolate had a GVV motif but this did not affect its sensitivity to T-20. Therefore, T-20 inhibited subtype C viruses despite significant genetic differences in the **HR2** region and there was no evidence for baseline resistance to T-20. These data suggest that T-20 would be highly effective in patients with **HIV**-1 subtype C infection, including those failing existing antiretroviral drug regimens.

L19 ANSWER 41 OF 59 MEDLINE on STN

2004282635. PubMed ID: 15184046. Suppression of SARS-CoV entry by peptides corresponding to heptad regions on spike glycoprotein. Yuan Kehu; Yi Ling; Chen Jian; Qu Xiuxia; Qing Tingting; Rao Xi; Jiang Pengfei; Hu Jianhe; Xiong Zikai; Nie Yuchun; Shi Xuanling; Wang Wei; Ling Chen; Yin Xiaolei; Fan Keqiang; Lai Luhua; Ding Mingxiao; Deng Hongkui. (Department of Cell Biology and Genetics, College of Life Sciences, Peking University, Beijing 100871, PR China.) Biochemical and biophysical research communications, (2004 Jul 2) Vol. 319, No. 3, pp. 746-52. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Heptad repeat regions (**HR1** and **HR2**) are highly conserved sequences located in the glycoproteins of enveloped viruses. They form a six-helix bundle structure and are important in the process of virus fusion. Peptides derived from the HR regions of some viruses have been shown to inhibit the entry of these viruses. SARS-CoV was also predicted to have **HR1** and **HR2** regions in the S2 protein. Based on this prediction, we designed 25 peptides and screened them using a **HIV**-luc/SARS pseudotyped virus assay. Two peptides, **HR1**-1 and **HR2**-18, were identified as potential inhibitors, with EC(50) values of 0.14 and 1.19microM, respectively. The inhibitory effects of these peptides were validated by the wild-type SARS-CoV assay. **HR1**-1 and **HR2**-18 can serve as functional probes for dissecting the fusion mechanism of SARS-CoV and also provide the potential of further identifying potent inhibitors for SARS-CoV entry.

L19 ANSWER 42 OF 59 MEDLINE on STN

2004235473. PubMed ID: 15113923. CD4-induced T-20 binding to **human immunodeficiency virus** type 1 gp120 blocks interaction with the CXCR4 coreceptor. Yuan Wen; Craig Stewart; Si Zhihai; Farzan Michael; Sodroski Joseph. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA.) Journal of virology, (2004 May) Vol. 78, No. 10, pp. 5448-57. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The synthetic peptide T-20, which corresponds to a sequence within the C-terminal heptad repeat region (**HR2**) of the **human immunodeficiency virus** type 1 (**HIV**-1) gp41 envelope glycoprotein, potently inhibits viral membrane fusion and entry. Although T-20 is thought to bind the

N-terminal heptad repeat region (**HR1**) of gp41 and interfere with gp41 conformational changes required for membrane fusion, coreceptor specificity determined by the V3 loop of gp120 strongly influences the sensitivity of **HIV**-1 variants to T-20. Here, we show that T-20 binds to the gp120 glycoproteins of **HIV**-1 isolates that utilize CXCR4 as a coreceptor in a manner determined by the sequences of the gp120 V3 loop. T-20 binding to gp120 was enhanced in the presence of soluble CD4. Analysis of T-20 binding to gp120 mutants with variable loop deletions and the reciprocal competition of T-20 and particular anti-gp120 antibodies suggested that T-20 interacts with a gp120 region near the base of the V3 loop. Consistent with the involvement of this region in coreceptor binding, T-20 was able to block the interaction of gp120-CD4 complexes with the CXCR4 coreceptor. These results help to explain the increased sensitivity of CXCR4-specific **HIV**-1 isolates to the T-20 peptide. Interactions between the gp41 **HR2** region and coreceptor-binding regions of gp120 may also play a role in the function of the **HIV**-1 envelope glycoproteins.

L19 ANSWER 43 OF 59 MEDLINE on STN

2004219247. PubMed ID: 15117459. Are fusion inhibitors active against all **HIV** variants?. Poveda Eva; Rodes Berta; Toro Carlos; Soriano Vincent. (Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain.) AIDS research and human retroviruses, (2004 Mar) Vol. 20, No. 3, pp. 347-8. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Genetic sequence alignment of the transmembrane region from **HIV**-1 group O and **HIV**-2 isolates was performed to examine their potential susceptibility to fusion inhibitors enfuvirtide (T-20) and T-1249. A high genetic diversity within the HRI and **HR2** domains was found, which should compromise any antiviral effect of T-20 on **HIV**-2 and **HIV**-1 group O viruses. However, conserved sequences in the gp41 regions from **HIV**-1 group O involved in T-1249 susceptibility might result in a much broader antiviral effect of T-1249 on **HIV**-1 variants. In contrast, genetic diversity in those regions make unlikely any activity of these compounds on **HIV**-2.

L19 ANSWER 44 OF 59 MEDLINE on STN

2004175337. PubMed ID: 15051887. Small-molecule inhibitors of **HIV**-1 entry block receptor-induced conformational changes in the viral envelope glycoproteins. Si Zhihai; Madani Navid; Cox Jason M; Chruma Jason J; Klein Jeffrey C; Schon Arne; Phan Ngoc; Wang Liping; Biorn Alyssa C; Cocklin Simon; Chaiken Irwin; Freire Ernesto; Smith Amos B 3rd; Sodroski Joseph G. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, MA 02115, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2004 Apr 6) Vol. 101, No. 14, pp. 5036-41. Electronic Publication: 2004-03-29. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB When interacting with the CD4 receptor, the **HIV** gp120 envelope glycoprotein undergoes conformational changes that allow binding to the chemokine receptor. Receptor binding is proposed to lead to conformational changes in the gp41 transmembrane envelope glycoprotein involving the creation and/or exposure of a coiled coil consisting of three heptad repeat (HR) sequences. The subsequent interaction of the **HR2** region of gp41 with this coiled coil results in the assembly of a six-helix bundle that promotes the fusion of the viral and target cell membranes. Here we show that CD4 binding to gp120 induces the formation and/or exposure of the gp41 **HR1** coiled coil in a process that does not involve gp120 shedding and that depends on the proteolytic maturation of the gp160 envelope glycoprotein precursor. Importantly, BMS-806 and related **HIV**-1 entry inhibitors bind gp120 and block the CD4 induction of **HR1** exposure without significantly affecting CD4 binding. Moreover, these compounds do not disrupt gp120-chemokine receptor binding or the

HR1-HR2 interaction within gp41. These studies thus define a receptor-induced conformational rearrangement of gp120-gp41 that is important for both CD4-dependent and CD4-independent HIV-1 entry and is susceptible to inhibition by low-molecular-weight compounds.

L19 ANSWER 45 OF 59 MEDLINE on STN

2004151843. PubMed ID: 15043961. Interaction between heptad repeat 1 and 2 regions in spike protein of SARS-associated coronavirus: implications for virus fusogenic mechanism and identification of fusion inhibitors. Liu Shuwen; Xiao Gengfu; Chen Yibang; He Yuxian; Niu Jinkui; Escalante Carlos R; Xiong Huabao; Farmar James; Debnath Asim K; Tien Po; Jiang Shibo. (Lindsley F Kimball Research Institute, New York Blood Center, New York, NY 10021, USA.) Lancet, (2004 Mar 20) Vol. 363, No. 9413, pp. 938-47. Journal code: 2985213R. E-ISSN: 1474-547X. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Studies on the fusion-inhibitory peptides derived from the heptad repeat 1 and 2 (HR1 and HR2) regions of the HIV-1 envelope glycoprotein gp41 provided crucial information on the viral fusogenic mechanism. We used a similar approach to study the fusogenic mechanism of severe-acute-respiratory-syndrome-associated coronavirus (SARS-CoV). METHODS: We tested the inhibitory activity against infection of two sets of peptides corresponding to sequences of SARS-CoV spike protein HR1 and HR2 regions and investigated the interactions between the HR1 and HR2 peptides by surface plasmon resonance, sedimentation equilibration analysis, circular dichroism, native polyacrylamide-gel electrophoresis, size exclusion high-performance liquid chromatography, and computer-aided homology modelling and molecule docking analysis. FINDINGS: One peptide, CP-1, derived from the HR2 region, inhibited SARS-CoV infection in the micromolar range. CP-1 bound with high affinity to a peptide from the HR1 region, NP-1. CP-1 alone had low alpha-helicity and self-associated to form a trimer in phosphate buffer (pH 7.2). CP-1 and NP-1 mixed in equimolar concentrations formed a six-helix bundle, similar to the fusogenic core structure of HIV-1 gp41. INTERPRETATION: After binding to the target cell, the transmembrane spike protein might change conformation by association between the HR1 and HR2 regions to form an oligomeric structure, leading to fusion between the viral and target-cell membranes. At the prefusion intermediate state, CP-1 could bind to the HR1 region and interfere with the conformational changes, resulting in inhibition of SARS-CoV fusion with the target cells. CP-1 might be modifiable to increase its anti-SARS-CoV activity and could be further developed as an antiviral agent for treatment or prophylaxis of SARS-CoV infection.

L19 ANSWER 46 OF 59 MEDLINE on STN

2004107891. PubMed ID: 14998221. Enfuvirtide, a new fusion inhibitor for therapy of human immunodeficiency virus infection. Hardy Helene; Skolnik Paul R. (Center for HIV/AIDS Care and Research, Boston Medical Center, Massachusetts 02118, USA.. helene.hardy@bmc.org) Pharmacotherapy, (2004 Feb) Vol. 24, No. 2, pp. 198-211. Journal code: 8111305. ISSN: 0277-0008. Pub. country: United States. Language: English.

AB Enfuvirtide is the first fusion inhibitor to be approved by the Food and Drug Administration for the treatment of chronic human immunodeficiency virus (HIV) infection in adults and children 6 years and older. The drug is a synthetic peptide derived from a naturally occurring amino acid sequence known as heptad repeat 2 (HR2) found in gp41, a viral transmembrane glycoprotein that facilitates fusion with host cells. By mimicking the activity of HR2 and competitively binding to a second region of gp41, heptad repeat 1 (HR1), enfuvirtide prevents interaction between HR1 and HR2 and inhibits the conformational change of gp41 that is necessary for fusion of virions to host cells. The safety and efficacy of enfuvirtide have been studied only in antiretroviral-experienced persons. Preliminary data from two multicenter phase III

clinical trials (T-20 versus Optimized Regimen Only [TORO 1, TORO 2]) suggest that the drug is safe and efficacious in heavily pretreated subjects through 24 weeks. By week 24, in TORO 1 and TORO 2, respectively, mean changes in **HIV** RNA concentrations of -1.7 and -1.4 log10 copies/ml were observed in subjects receiving enfuvirtide plus an optimized background (OB) regimen, compared with changes of -0.8 and -0.7 log10 copies/ml in subjects receiving an OB regimen alone. Resistance to enfuvirtide has been identified in vitro and in vivo. Most resistant variants contain mutations in the **HR1** region of gp41 (positions 36-45). In phase III clinical trials, numerous substitutions within this critical region were associated with faster time to virologic failure over 24 weeks. Overall, enfuvirtide appears to be well tolerated and acceptable to patients despite a high rate of injection site reactions (> 90%). Bacterial pneumonia and eosinophilia occurred more frequently in subjects taking enfuvirtide than in those taking an OB regimen alone in phase III trials; however, no causal relationship was established. Like most drugs with peptide structures, enfuvirtide appears to have a low potential for metabolic drug-drug interactions. The approved dosage is 90 mg twice/day by subcutaneous injection in adults and 2 mg/kg twice/day in children older than 6 years. Enfuvirtide is an addition to antiretroviral therapy since it targets a new step in the **HIV** life cycle. Given the complexity of its production and administration, however, it is likely to be most useful in antiretroviral-experienced patients.

L19 ANSWER 47 OF 59 MEDLINE on STN

2004041907. PubMed ID: 14741199. Fast folding of the **HIV**-1 and SIV gp41 six-helix bundles. Marti Daniel N; Bjelic Sasa; Lu Min; Bosshard Hans Rudolf; Jelesarov Ilian. (Biochemisches Institut der Universitat Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.) Journal of molecular biology, (2004 Feb 6) Vol. 336, No. 1, pp. 1-8. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: England: United Kingdom. Language: English.

AB Human (**HIV**-1) and simian (SIV) immunodeficiency virus fusion with the host cell is promoted by the receptor-triggered refolding of the gp41 envelope protein into a stable trimer-of-hairpins structure that brings viral and cellular membranes into close proximity. The core of this hairpin structure is a six-helix bundle in which an inner homotrimeric coiled coil is buttressed by three antiparallel outer **HR2** helices. We have used stopped-flow circular dichroism spectroscopy to characterize the unfolding and refolding kinetics of the six-helix bundle using the **HIV**-1 and SIV N34(L6)C28 polypeptides. In each case, the time-course of ellipticity changes in refolding experiments is well described by a simple two-state model involving the native trimer and the unfolded monomers. The unfolding free energy of the **HIV**-1 and SIV trimers and their urea dependence calculated from kinetic data are in very good agreement with data measured directly by isothermal unfolding experiments. Thus, formation of the gp41 six-helix bundle structure involves no detectable population of stable, partly folded intermediates. Folding of **HIV**-1 N34(L6)C28 is five orders of magnitudes faster than folding of its SIV counterpart in aqueous buffer: k(on),(**HIV**-1)=1.3 x 10(15)M(-2)s(-1) versus k(on),(SIV)=1.1 x 10(10)M(-2)s(-1). The unfolding rates are similar: k(off),(**HIV**-1)=1.1 x 10(-5)s(-1) versus k(off),(SIV=)5.7 x 10(-4)s(-1). Kinetic m-values indicate that the transition state for folding of the **HIV**-1 protein is significantly more compact than the transition state of the SIV protein. Replacement of a single SIV threonine by isoleucine corresponding to position 573 in the **HIV**-1 sequence significantly stabilizes the protein and renders the folding rate close to that of the **HIV**-1 protein yet without making the transition state of the mutant as compact as that of the **HIV**-1 protein. Therefore, the overall reduction of surface exposure in the high-energy transition state seems not to account for different folding rates. While the available biological evidence suggests that refolding of the gp41 protein

is slow, our study implies that structural elements outside the trimer-of-hairpins limit the rate of **HIV**-1 fusion kinetics.

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2003610850. PubMed ID: 14694113. Role of the ectodomain of the gp41 transmembrane envelope protein of **human immunodeficiency virus** type 1 in late steps of the membrane fusion process. Bar Severine; Alizon Marc. (Department of Cell Biology, Institut Cochin, INSERM U567, CNRS UMR8104, 75014 Paris, France.) Journal of virology, (2004 Jan) Vol. 78, No. 2, pp. 811-20. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The membrane fusion process mediated by the gp41 transmembrane envelope glycoprotein of the **human immunodeficiency virus** type 1 (**HIV**-1) was addressed by a flow cytometry assay detecting exchanges of fluorescent membrane probes (DiI and DiO) between cells expressing the **HIV**-1 envelope proteins (Env) and target cells. Double-fluorescent cells were detected when target cells expressed the type of chemokine receptor, CXCR4 or CCR5, matching the type of gp120 surface envelope protein, X4 or R5, respectively. Background levels of double-fluorescent cells were observed when the gp120-receptor interaction was blocked by AMD3100, a CXCR4 antagonist. The L568A mutation in the N-terminal heptad repeat (**HR1**) of gp41 resulted in parallel inhibition of the formation of syncytia and double-fluorescent cells, indicating that gp41 had a direct role in the exchange of fluorescent probes. In contrast, three mutations in the loop region of the gp41 ectodomain, located on either side of the Cys-(X)(5)-Cys motif (W596 M and W610A) or at the distal end of **HR1** (D589L), had limited or no apparent effect on membrane lipid mixing between Env(+) and target cells, while they blocked formation of syncytia and markedly reduced the exchanges of cytoplasmic fluorescent probes. The loop region could therefore have a direct or indirect role in events occurring after the merging of membranes, such as the formation or dilation of fusion pores. Two types of inhibitors of **HIV**-1 entry, the gp41-derived peptide T20 and the betulinic acid derivative RPR103611, had limited effects on membrane exchanges at concentrations blocking or markedly reducing syncytium formation. This finding confirmed that T20 can inhibit the late steps of membrane fusion (post-lipid mixing) and brought forth an indirect argument for the role of the gp41 loop region in these steps, as mutations conferring resistance to RPR103611V were mapped in this region (I595S or L602H).

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2003565061. PubMed ID: 14651977. Mutations in gp41 and gp120 of **HIV**-1 isolates resistant to hexa-arginine neomycin B conjugate. Borkow Gadi; Lara Humberto Herman; Lapidot Aviva. (Department of Organic Chemistry, The Weizmann Institute of Science, 76100, Rehovot, Israel.) Biochemical and biophysical research communications, (2003 Dec 26) Vol. 312, No. 4, pp. 1047-52. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Aminoglycoside-arginine conjugates (AACs) inhibit **HIV**-1 replication and act as Tat antagonists. AACs compete with monoclonal antibody binding to CXCR4, compete with SDF-1alpha and **HIV**-1 gp120 cellular uptake, indicating that they interfere with initial steps of **HIV**-1 infection. We here present the selection of **HIV**-1 isolates resistant to hexa-arginine neomycin B conjugate (NeoR6), the most potent anti-**HIV**-1 AAC. We found in the NeoR6-resistant isolates the following mutations in gp120: I339T in the C3 region, S372L in the V4 region, and Q395K in the C4 region; and in gp41: S668R and F672Y in the 'heptad repeat' 2 (**HR2**) region. These findings strongly suggest that NeoR6 obstructs **HIV**-1 replication by interfering with the fusion step, dependent on both conformational changes in gp120 following CD4 and CXCR4 interaction, as well as by conformational changes in gp41 induced by **HR1** and **HR2** interaction. The AACs may thus represent a novel family of fusion

inhibitors.

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2003316319. PubMed ID: 12829845. Multiple interactions across the surface of the gp120 core structure determine the global neutralization resistance phenotype of **human immunodeficiency virus** type 1. Bouma Peter; Leavitt Maria; Zhang Peng Fei; Sidorov Igor A; Dimitrov Dimiter S; Quinnan Gerald V Jr. (Division of Tropical Public Health, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, USA.) Journal of virology, (2003 Jul) Vol. 77, No. 14, pp. 8061-71. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.
AB Resistance to neutralization is an important characteristic of primary isolates of **human immunodeficiency virus** type 1 (**HIV**-1) that relates to the potential for successful vaccination to prevent infection and use of immunotherapeutics for treatment of established infection. In order to further elucidate mechanisms responsible for neutralization resistance, we studied the molecular mechanisms that determine the resistance of the primary virus isolate of the strain **HIV**-1 MN to neutralization by soluble CD4 (sCD4). As is the case for the global neutralization resistance phenotype, sCD4 resistance depended upon sequences in the amino-terminal heptad repeat region of gp41 (**HR1**), as well as on multiple functional interactions within the envelope complex. The functional interactions that determined the resistance included interactions between the variable loop 1 and 2 (V1/V2) region and sequences in or near the CD4 binding site (CD4bs) and with the V3 loop. Additionally, the V3 loop region was found to interact functionally with sequences in the outer domain of gp120, distant from the CD4bs and coreceptor-binding site, as well as with a residue thought to be located centrally in the coreceptor-binding site. These and previous results provide the basis for a model by which functional signals that determine the neutralization resistance, high-infectivity phenotype depend upon interactions occurring across the surface of the gp120 core structure and involving variable loop structures and gp41. This model should be useful in efforts to define epitopes that may be important for primary virus neutralization.

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2003215499. PubMed ID: 12736375. The LLSGIV stretch of the N-terminal region of **HIV**-1 gp41 is critical for binding to a model peptide, T20. Trivedi Vishwa Deo; Cheng Shu-Fang; Wu Cheng-Wei; Karthikeyan Radhakrishnan; Chen Chen-Jui; Chang Ding-Kwo. (Institute of Chemistry, Academia Sinica, Taipei 11529, Taiwan.) Protein engineering, (2003 Apr) Vol. 16, No. 4, pp. 311-7. Journal code: 8801484. ISSN: 0269-2139. Pub. country: England: United Kingdom. Language: English.
AB A number of peptides and peptide analogs derived from the membrane proximal region of gp41 ectodomain are found to be effective inhibitors of **human immunodeficiency virus** type 1 (**HIV**-1)-mediated fusion events. One of them, T20 (aa 638-673), was found disordered and sparingly soluble in water, but became soluble upon mixing with selected, structured peptides from the amino terminal heptad repeat (**HR1**) region of gp41 using a simple and sensitive method of reduction in the scattering of T20 suspension. From the results on mapping the locus of interaction with T20 by employing partially overlapping peptides derived from **HR1**, it was concluded that the LLSGIV segment was a critical docking site for the C-terminal peptide of gp41 in its putative inhibitory action consistent with a previous fluorescence study. It was also found that peptides capable of solubilizing T20 dispersion have a high content of helix, as well as beta-strand, conformation in aqueous solution. Specificity of T20/**HR1**-derived peptide binding was ascertained by using a scrambled sequence of a T20-active peptide and a plateau in scattering reduction of T20 suspension with variation in the concentration of a T20-active **HR1**

peptide. Implications on the mechanism of T20 inhibition and the sequence of folding of the gp41 core structure are discussed.

L19 ANSWER 52 OF 59 MEDLINE on STN
2003199173. PubMed ID: 12718536. The hydrophobic pocket contributes to the structural stability of the N-terminal coiled coil of **HIV** gp41 but is not required for six-helix bundle formation. Dwyer John J; Hasan Aisha; Wilson Karen L; White Jonathan M; Matthews Thomas J; Delmedico Mary K. (Trimeris, Inc., 3518 Westgate Drive, Durham, North Carolina 27707, USA.) Biochemistry, (2003 May 6) Vol. 42, No. 17, pp. 4945-53. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.
AB In models of **HIV** fusion, the glycoprotein gp41 is thought to form a six-helix bundle during viral fusion with the target cell. This bundle is comprised of three helical regions (from the heptad repeat 2, or **HR2**, region of gp41) bound to an inner, trimeric, coiled-coil core (from the **HR1** region). Although much has been learned about the structure and thermodynamics of this complex, the energetics of the isolated **HR1** self-associated oligomer remain largely unknown. By systematically studying self-association through a series of truncations based on a 51-mer **HR1** peptide (T865), we have identified amino acid segments which contribute significantly to the stability of the oligomeric **HR1** complex. Biophysical characterization of C-terminal truncations of T865 identifies a 10-15-amino acid region that is essential for **HR1** oligomerization. This region coincides with a hydrophobic pocket that provides important contacts for the interaction of **HR2** helices. Complete removal of this pocket abolishes **HR1** oligomerization. Despite the dramatic reduction in stability, the monomeric **HR1** peptides are still able to form stable six-helix bundles in the presence of **HR2** peptides. Truncations on the N-terminal side of T865 have little effect on oligomerization but significantly reduce the stability of the **HR1**-**HR2** six-helix bundle. Unlike the **HR2** binding site, which extends along a hydrophobic groove on the **HR1** oligomer, the residues that are critical for **HR1** oligomerization are concentrated in a 10-15-amino acid region. These results demonstrate that there are localizations of binding energy, or "hot spots", in the self-association of peptides derived from the **HR1** region of gp41.

L19 ANSWER 53 OF 59 MEDLINE on STN
2003152836. PubMed ID: 12615056. Both heptad repeats of human respiratory syncytial virus fusion protein are potent inhibitors of viral fusion. Wang Enxiu; Sun Xiao'ou; Qian Yuan; Zhao Linqing; Tien Po; Gao George F. (Department of Molecular Virology and Bio-Engineering, Institute of Microbiology, Chinese Academy of Sciences, Zhongguancun Beiyitiao, Beijing 100080, China.) Biochemical and biophysical research communications, (2003 Mar 14) Vol. 302, No. 3, pp. 469-75. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB Heptad repeat regions (**HR1** and **HR2**) are highly conserved peptides located in F(1) of paramyxovirus envelope proteins. They are important in the process of virus fusion and form six-helix bundle structure (trimer of **HR1** and **HR2** heterodimer) post-fusion, similar to those found in the fusion proteins of other enveloped viruses, such as retrovirus **HIV**. Both **HR1** and **HR2** show potent inhibition for virus fusion in some members of paramyxovirus. However, in other members, only **HR2** gives strong inhibition whereas **HR1** does not. Human respiratory syncytial virus (hRSV) is a member of paramyxovirus and its crystal structure of **HR1** and **HR2** six-helix bundle was solved lately. Although hRSV **HR2** inhibition was reported, nevertheless the effect of **HR1** on virus fusion is not known. In this study, hRSV **HR1** and **HR2** were expressed as fusion protein separately in Escherichia coli system and their complex assembly and virus fusion inhibition effect have been analysed. It shows that both **HR1** and **HR2** (in the fusion form with 50-amino-acid fusion partner) of hRSV F protein give strong inhibition on virus fusion (IC(50)

values are 1.68 and 2.93 microM, respectively) and they form stable six-helix bundle in vitro with both in the fusion protein form.

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2002726677. PubMed ID: 12444251. Sensitivity of **HIV**-1 to entry inhibitors correlates with envelope/coreceptor affinity, receptor density, and fusion kinetics. Reeves Jacqueline D; Gallo Stephen A; Ahmad Navid; Miamidian John L; Harvey Phoebe E; Sharron Matthew; Pohlmann Stefan; Sfakianos Jeffrey N; Derdeyn Cynthia A; Blumenthal Robert; Hunter Eric; Doms Robert W. (Department of Microbiology, University of Pennsylvania, 225 Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA 19104, USA.. jreeves@mail.med.upenn.edu) . Proceedings of the National Academy of Sciences of the United States of America, (2002 Dec 10) Vol. 99, No. 25, pp. 16249-54. Electronic Publication: 2002-11-20. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB **HIV** entry inhibitors include coreceptor antagonists and the fusion inhibitor T-20. T-20 binds the first helical region (**HR1**) in the gp41 subunit of the viral envelope (Env) protein and prevents conformational changes required for membrane fusion. **HR1** appears to become accessible to T-20 after Env binds CD4, whereas coreceptor binding is thought to induce the final conformational changes that lead to membrane fusion. Thus, T-20 binds to a structural intermediate of the fusion process. Primary viruses exhibit considerable variability in T-20 sensitivity, and determinants outside of **HR1** can affect sensitivity by unknown mechanisms. We studied chimeric Env proteins containing different V3 loop sequences and found that gp120coreceptor affinity correlated with T-20 and coreceptor antagonist sensitivity, with greater affinity resulting in increased resistance to both classes of entry inhibitors. Enhanced affinity resulted in more rapid fusion kinetics, reducing the time during which Env is sensitive to T-20. Reduced coreceptor expression levels also delayed fusion kinetics and enhanced virus sensitivity to T-20, whereas increased coreceptor levels had the opposite effect. A single amino acid change (K421D) in the bridging sheet region of the primary virus strain YU2 reduced affinity for CCR5 and increased T-20 sensitivity by about 30-fold. Thus, mutations in Env that affect receptor engagement and membrane fusion rates can alter entry inhibitor sensitivity. Because coreceptor expression levels are typically limiting in vivo, individuals who express lower coreceptor levels may respond more favorably to entry inhibitors such as T-20, whose effectiveness we show depends in part on fusion kinetics.

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2002430478. PubMed ID: 12186891. C-Terminal gp40 peptide analogs inhibit feline immunodeficiency virus: cell fusion and virus spread. Medinas R J; Lambert D M; Tompkins W A. (Immunology Program, North Carolina State University, Raleigh 27606, USA.) Journal of virology, (2002 Sep) Vol. 76, No. 18, pp. 9079-86. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The envelope glycoprotein of **human immunodeficiency virus** type 1 (**HIV**-1), gp160, is synthesized as a protein precursor that when proteolytically cleaved yields two subunits, gp120 and gp41. gp120 is the surface glycoprotein on **HIV**-1 responsible for binding to CD4, and gp41 is the transmembrane glycoprotein involved in the membrane fusion process. gp41 is divided into the N-terminal fusion peptide, the heptad repeat 1 (**HR1**) and **HR2** regions, and the C-terminal transmembrane region, which are collectively responsible for virus fusion and entry into the cell. Synthetic peptides derived from the **HR2** and **HR1** regions of **HIV**-1(LAI) have been shown to prevent virus-cell fusion and infection in vitro. In phase II clinical trials in **HIV** patients, data revealed that T20 has antiviral efficacy and is well tolerated. Similar results were obtained in vitro with **HIV**-2 and simian immunodeficiency virus, supporting the conservation of the gp41 ectodomain among lentiviruses.

Feline immunodeficiency virus (FIV) infection in the cat has been used as a model to develop potential antivirals for **HIV**. To determine if synthetic gp40 analogs capable of inhibiting FIV infection could be identified, 15 overlapping 35-amino-acid peptides derived from the C-terminal **HR2** domain of FIV gp40 were synthesized. These peptides were tested for efficacy against FIV in a syncytium-forming assay with FIV-infected CrFK cells and HeLa cells expressing the FIV receptor CXCR4. Several peptides exhibited activity at the nanogram level. Antiviral activity was confirmed by suppression of reverse transcriptase in a FIV feline CD4(+)-T-cell (FCD4-B) acute-infection assay. These data demonstrate that synthetic peptides derived from the **HR2** domain of the FIV gp41 protein are effective inhibitors of FIV infection.

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2002417436. PubMed ID: 12172081. Variability of critical epitopes within **HIV**-1 heptad repeat domains for selected entry inhibitors in **HIV**-infected populations worldwide [corrected]. Hanna Sheri L; Yang Chunfu; Owen Sherry M; Lal Renu B. (HIV Immunology and Diagnostics Branch, Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA.) AIDS (London, England), (2002 Aug 16) Vol. 16, No. 12, pp. 1603-8. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Two of the fusion inhibitors T-20 and 5-helix polypeptide have been shown to be potent inhibitors of cell-to-cell fusion and are currently under investigation as therapy for **HIV**-1. OBJECTIVES: To examine variability of **HIV**-1 gp41 heptads repeat regions (**HR1** and **HR2**), with special emphasis on the presence of T-20 resistance mutations and 5-helix variability at critical epitopes, in treatment-naive patients infected with diverse **HIV**-1 subtypes from different geographic regions. METHODS: A total of 150 specimens representing **HIV**-1 group M subtypes (A-G) from persons naive to **HIV**-1 viral entry inhibitor therapy were used to amplify and sequence a 506 bp segment of transmembrane protein. RESULTS: In general, both **HR1** (a.a. 540-593) and **HR2** (a.a. 628-673) domains were highly conserved. Sequence analysis of the T-20 resistant domain (a.a. 547-549, GIV) revealed that 99% of the specimens (149 of 150) carried a T-20 sensitive genotype. The critical epitopes involved in the 5-helix interaction include residues at positions 628W, 631W, 635I, 638Y, 642I, 645L, 649S, 652Q, 656N, and 659E. Analysis of the 150 specimens revealed that all had identical residues at six of these positions, whereas two positions had minor variations (635 and 649) and two (645 and 659) appeared to have subtype-specific substitutions. CONCLUSIONS: This data indicates that there is limited resistance to T-20 in these worldwide populations and that the critical epitopes for effective 5-helix binding are highly conserved across all subtypes. Taken together, these data suggest that T-20 and 5-helix should provide useful additives to current antiretroviral therapy for clinical management of **HIV** disease.

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2002293201. PubMed ID: 12019106. Emergence of resistant **human immunodeficiency virus** type 1 in patients receiving fusion inhibitor (T-20) monotherapy. Wei Xiping; Decker Julie M; Liu Hongmei; Zhang Zee; Arani Ramin B; Kilby J Michael; Saag Michael S; Wu Xiaoyun; Shaw George M; Kappes John C. (Howard Hughes Medical Institute, Department of Medicine, University of Alabama at Birmingham, 35294, USA.) Antimicrobial agents and chemotherapy, (2002 Jun) Vol. 46, No. 6, pp. 1896-905. Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB The synthetic peptide T-20 (enfuvirtide) represents the first of a new class of antiretroviral compounds to demonstrate in vivo potency by targeting a step in viral entry. T-20 inhibits a conformational change in the **human immunodeficiency virus** type 1 (**HIV**-1) transmembrane glycoprotein (gp41) that is required for fusion between **HIV**-1 and target

cell membranes. The initial phase I clinical trial of T-20 treatment for **HIV**-infected patients thus provided a unique opportunity to evaluate the emergence of resistant virus in vivo to this novel class of antiretroviral agents. All four patients who received an intermediate dose of T-20 (30 mg twice daily) had an initial decline in plasma viral load over the first 10 days but a rising trend by day 14, suggestive of selection for resistant virus. Plasma virus derived from patients enrolled in all dosage groups of the phase I T-20 trial was analyzed by population sequencing before and after treatment. While no mutations were found within a highly conserved 3-amino-acid sequence (GIV) known to be critical for fusion at baseline, after 14 days of therapy, virus from one patient in the 30-mg dose group (30-1) developed a mutation in this motif, specifically an aspartic acid (D) substitution for glycine (G) at position 36. Multiple env clones were derived from the plasma virus of all four patients in the 30-mg dosage group. Sequence analysis of 49 clones derived from the plasma of patient 30-1 on day 14 revealed that 25 clones contained the G36D mutation, while 8 contained the V38A mutation. Dual mutations involving G36D and other residues within the **HR1** domain were also identified. In 5 of the 49 env clones, other mutations involving residues 32 (Q32R or Q32H) and 39 (Q39R) were found in combination with G36D. Cloned env sequences derived from the plasma virus of subject 30-3 also had single mutations in the GIV sequence (V38M and I37V) detectable following therapy with T-20. The plasma virus from subjects 30-2 and 30-4 did not contain changes within the GIV sequence. To analyze the biological resistance properties of these mutations, we developed a novel single-cycle **HIV**-1 entry assay using JC53BL cells which express beta-galactosidase and luciferase under control of the **HIV**-1 long terminal repeat. Full-length env clones were derived from the plasma virus of patients 30-1 and 30-3 and used to generate pseudotyped virus stocks. The mean 50% inhibition concentrations (IC(50)s) for mutants G36D and V38A (patient 30-1) were 2.3 microg/ml and 11.2 microg/ml, respectively, statistically significant increases of 9.1- and 45-fold, respectively, compared with those of wild-type Env. The IC(50) for the V38 M mutation (patient 30-3) was 7.6 microg/ml, an 8-fold increase compared with that of the wild type. The I37V mutation resulted in an IC(50) 3.2-fold greater than that of the wild type. Envs with double mutations (Q32R plus G36D and Q32H plus G36D) exhibited a level of resistance similar to that of G36D alone. These findings provide the first evidence for the rapid emergence of clinical resistance to a novel class of **HIV**-1 entry inhibitors and may be relevant to future treatment strategies involving these agents.

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2001462471. PubMed ID: 11507206. Sensitivity of **human immunodeficiency virus** type 1 to fusion inhibitors targeted to the gp41 first heptad repeat involves distinct regions of gp41 and is consistently modulated by gp120 interactions with the coreceptor. Derdeyn C A; Decker J M; Sfakianos J N; Zhang Z; O'Brien W A; Ratner L; Shaw G M; Hunter E. (Department of Microbiology, Birmingham, Alabama 35294, USA.) Journal of virology, (2001 Sep) Vol. 75, No. 18, pp. 8605-14. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB T-20 is a synthetic peptide that corresponds to 36 amino acids within the C-terminal heptad repeat region (**HR2**) of **human immunodeficiency virus** type 1 (**HIV**-1) gp41. T-20 has been shown to potently inhibit viral replication of **HIV**-1 both in vitro and in vivo and is currently being evaluated in a Phase III clinical trial. T-649 is an inhibitory peptide that also corresponds to 36 amino acids within **HR2**. This sequence overlaps the T-20 sequence but is shifted 10 residues toward the N terminus of gp41. Both inhibitors are thought to exert their antiviral activity by interfering with the conformational changes that occur within gp41 to promote membrane fusion following gp120 interactions with CD4 and coreceptor molecules. We have shown previously that coreceptor

specificity defined by the V3 loop of gp120 modulates sensitivity to T-20 and that a critical region within the N-terminal heptad repeat (**HR1**) of gp41 is the major determinant of sensitivity (C. A. Derdeyn et al., J. Virol. 74:8358-8367, 2000). This report shows that (i) regions within gp41 distinct from those associated with T-20 sensitivity govern the baseline sensitivity to T-649 and (ii) T-649 sensitivity of chimeric viruses that contain sequences derived from CXCR4- and CCR5-specific envelopes is also modulated by coreceptor specificity. Moreover, the pattern of sensitivity of CCR5-specific chimeras with only minor differences in their V3 loop was consistent for both inhibitors, suggesting that the individual affinity for coreceptor may influence accessibility of these inhibitors to their target sequence. Finally, an analysis of the sensitivity of 55 primary, inhibitor-naive **HIV**-1 isolates found that higher concentrations of T-20 ($P < 0.001$) and T-649 ($P = 0.016$) were required to inhibit CCR5-specific viruses compared to viruses that utilize CXCR4. The results presented here implicate gp120-coreceptor interactions in driving the complex conformational changes that occur in gp41 to promote fusion and entry and suggest that sensitivity to different **HR1**-directed fusion inhibitors is governed by distinct regions of gp41 but is consistently modulated by coreceptor specificity.

L19 ANSWER 59 OF 59 MEDLINE on STN
2001201555. PubMed ID: 11153086. Monoclonal antibodies that bind to the core of fusion-active glycoprotein 41. Chen C H; Greenberg M L; Bolognesi D P; Matthews T J. (Department of Microbiology, Meharry Medical College, Nashville, Tennessee 37208, USA.. cchen@mail.mmc.edu) . AIDS research and human retroviruses, (2000 Dec 10) Vol. 16, No. 18, pp. 2037-41. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The heptad repeat regions **HR1** and **HR2** of **HIV**-1 gp41 can associate to form heterooligomers through helical coil-coil interactions that are believed to play a key role in virus-induced membrane fusion. The **HR1**/**HR2** complex was proposed to be the core structure of the fusion-active conformation of gp41. Here, we show that two human monoclonal antibodies, Fab-d and 50-69, specifically recognize the putative fusion-active conformation of gp41. Fab-d binding requires the interaction between the **HR1** and **HR2** regions of gp41. The reactivity of human monoclonal antibody 50-69 to the C terminus of the **HR1** sequence is dependent on the helical structure of **HR1**. It appears that **HR2** is able to interact with **HR1** and, subsequently, induce an epitope in **HR1** that is required for 50-69 binding. Mutations that disrupt the helical structure of **HR1** significantly compromise Fab-d and 50-69 binding. Although the epitopes are not identical, the ability of Fab-d to partially compete with 50-69 binding suggests a close proximity of the two epitopes. Antibodies that are able to interact with the core of the putative fusion-active gp41 may be useful in further unveiling the mechanism of **HIV**-induced membrane fusion.

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=> d his

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     FILE 'USPATFULL' ENTERED AT 02:55:22 ON 02 OCT 2006
                E DELMEDICO MARY KAY/IN
L1            1 S E3
                E DWYER JOHN/IN
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L2            31 S E3-E11
L3             2 S L2 AND (HR1 OR HR2)
L4             1 S L3 NOT L1

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L5             4 S E3
                E DWYER JOHN/IN
                E DWYER J/IN
L6            13 S E3
L7             2 S L6 AND (HR1 OR HR2)

     FILE 'MEDLINE' ENTERED AT 02:58:37 ON 02 OCT 2006
                E DELMEDICO M K/AU
L8             2 S E3 OR E4
                E DWYER JOHN/AU
L9             5 S E3
L10            5 S L9 NOT L8

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L11        47774 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12          136 S L11 AND (HR1 OR HR2)
L13            8 S L12 AND (HR1/CLM OR HR2/CLM)
L14            7 S L13 NOT L1

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L15        23476 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L16           13 S L15 AND (HR1 OR HR2)
L17           10 S L16 NOT L5

     FILE 'MEDLINE' ENTERED AT 03:01:16 ON 02 OCT 2006
L18       168740 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L19           59 S L18 AND (HR1 OR HR2)

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STN INTERNATIONAL LOGOFF AT 03:02:02 ON 02 OCT 2006
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